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SPIRO-AMINO BARBITURIC ACIDS

A THESIS

Presented to

the Faculty of the Graduate Division

By

Phillip Michael Daugherty

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

May 1957

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SPIRO-AMINO BARBITURIC ACIDS

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Date of Approval by Chairman: May 31, 1957

ACKNOWLEDGMENTS

The author is indebted to Dr. James A. Stanfield for his supervision and invaluable guidance during the course of this research. He is also indebted to Dr. Jack Hine and Dr. Loyd D. Frashier who served on the reading committee.

The financial assistance afforded by the Engineering Experiment Station through employment while pursuing this effort and through sponsorship of a portion of the synthetic work under the project designation, E-124, is appreciated. The author is also grateful for the financial aid extended through a National Institute of Health Grant (Engineering Experiment Station, Project B-114) for the portion of the work on the hydrolysis rate determinations.

The encouragement of an understanding wife and family is greatly appreciated.

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ABSTRACT

The object of this research was to investigate methods of preparing certain new derivatives of barbituric acid and to obtain information concerning the stability of these and related materials. A number of the desired structures, which incorporate a nitrogen containing spiro-ring system on barbituric acid, have been realized.

In the attempt to prepare these compounds the first method investigated involved the reaction of sodium diethyl malonate with suitable bis-(2-haloethyl)amines. It was planned to condense the resulting diethyl N-alkylpiperidine-4,4-dicarboxylates with urea to yield the spiro-amino barbituric acids. However, upon attempting this reaction no product that could be identified as the desired ester was isolated.

Attempts to react two moles of dimethyl-2-chloroethylamine with a mole of sodium diethyl malonate in order to produce diethyl bis(2-dimethylaminoethyl)malonate were made. This substance was to have been condensed with urea (or related compounds) to give a disubstituted barbituric acid which would then be cyclized to give a spiro-amino barbituric acid. Although the reaction of one mole of the chloroethylamine with malonic ester proceeded satisfactorily, the second mole could not be introduced to any great extent.

The successful procedure consisted of the cleaving of the oxygen linkage in spirotetrahydropyran-4',5-barbituric acid (tetrahydropyran-4,5-spiro-2,4,5-triketohexahydropyrimidine) with hydrogen iodide, then condensing the resulting 5,5-bis(2-iodoethyl)barbituric acid with primary amines.

The spiro-amino barbituric acids listed in the following Table have been prepared by this method and have been characterized. In addition to these compounds, two other previously unreported spiro-barbituric acids, spirotetrahydropyran-4',5-thiobarbituric acid and spirotetrahydropyran-4',5-iminobarbituric acid were also prepared.

The relative rates of basic hydrolysis of a number of spiro-barbituric acids were determined and compared to the rate of hydrolysis of 5,5-diethylbarbituric acid under similar conditions. These rate data showed that both the unsubstituted five and six membered carbocyclic spiro-barbituric acids and spirotetrahydropyran-4',5-barbituric acid hydrolyzed at a much faster rate than did the 5,5-diethylbarbituric acid. By contrast the one spiro-amino barbituric acid studied hydrolyzed at a slower rate than did the 5,5-diethylbarbituric acid.

Recommendations for synthesizing some additional types of spiro-amino-barbituric acids were made. In addition it was recommended that further study of the rate of basic hydrolysis of derivatives of barbituric acids would be of value in determining the mechanism by which hydrolysis occurs and in establishing if a relationship exists between the stability of barbituric acid derivatives and their physiological activity.

Infrared spectra of these new spiro-amino barbituric acids (and of certain of the intermediates and by-products) were recorded using a Perkin-Elmer Model 21 double-beam spectrophotometer. From these infrared spectra it was interpreted that the probably structure of the spiro-amino barbituric acids was one of a dipolar ion, or inner salt structure.

Examinations of certain barbituric acids in the ultraviolet wavelength range have been made using a Beckman Model DK-2 recording spectrophotometer. The ultraviolet spectra indicate that the spiro-amino

Spiro-amino Barbiruric Acid

Barbituric Acid	M.P.[†]	Nitrogen	
		Calculated (%)	Found (%)
Spiro-1'-methylpiperidine-4',5-barbituric Acid	164-166	19.89	20.07[††]
Spiro-1'-ethylpiperidine-4',5-barbituric Acid	166-167.5	18.66	18.84
Spiro-1'-(2-hydroxyethyl)piperidine-4',5-barbituric Acid	277-278	17.42	17.46
Spiro-1'-allylpiperidine-4',5-barbituric Acid	134.5-135.5	17.71	17.85
Spiro-1'-isopropylpiperidine-4',5-barbituric Acid	143-145	17.49	17.42
Spiro-1'-n-butylpiperidine-4',5-barbituric Acid	174-175	16.59	16.66
Spiro-1'-cyclohexylpiperidine-4',5-barbituric Acid	194-196	15.04	14.96
Spiro-1'-phenylpiperidine-4',5-barbituric Acid	209-210	15.38	15.18
Spiro-1'-benzylpiperidine-4',5-barbituric Acid	172.5-173.5	14.63	14.61
Spiro-1'-o-tolylpiperidine-4',5-barbituric Acid	178-179	14.63	14.30
Spiro-1'-p-tolylpiperidine-4',5-barbituric Acid	157-158	14.63	14.68
Spiro-1'-(2-phenylethyl)piperidine-4',5-barbituric Acid	165-167	13.94	13.75

[†]Unless otherwise noted all melting points are in degrees centigrade and were determined using a Kofler hot-stage micro melting point apparatus, and, therefore, are corrected. The melting of the amino-barbituric acids is accompanied with decomposition and the melting point varies slightly with the rate of heating.

[††]Calculated for $C_9H_{13}N_3O_3$: C = 51.18 per cent; H = 6.20 per cent
Found: C = 51.45 per cent; H = 6.19 per cent

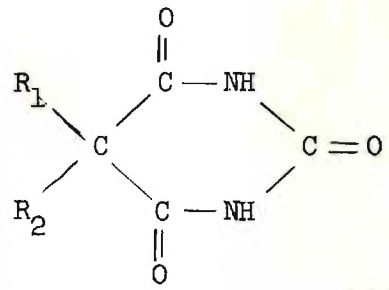
barbituric acids exist in aqueous solution in an ionic form such as would result if a proton were removed from the barbituric acid portion of the molecule. This shows the amino acid character of the compounds.

CHAPTER I

INTRODUCTION

The purpose of this research was to investigate methods of preparation of certain new derivatives of barbituric acid incorporating a nitrogen-containing spiro-ring system on barbituric acid and to examine some of the properties of these derivatives. It was believed that these compounds might possess definite, and perhaps valuable, physiological properties. A secondary purpose was to make some preliminary examinations of possible methods for studying rates of hydrolysis of derivatives of barbituric acids.

The cyclic diimides, prepared by condensing urea or thiourea with disubstituted malonic esters, form an important group of compounds which possess unusual physiological activity. Known commonly as barbiturates, these materials are derivatives of barbituric acid (Figure 1, $R_1 = R_2 = H$). The barbiturates have a depressant action on the central nervous system and are valuable sedatives and soporifics. The first barbiturate to be used successfully as a sedative was Veronal or Barbital (Figure 1a). This compound, first introduced in 1903, is still used for its effects on the nervous system. Since this time, many hundreds of derivates of barbituric acid have been prepared, including phenobarbital, amytal, nembutal, and seconal. These compounds are depicted in formulas b through e of Figure 1. A not too distant relative of these is pentothal sodium, (Figure 2) which is a valuable general anaesthetic, being used principally by intraveneous injection.



		R_1	R_2
a.	Veronal	C_2H_5	C_2H_5
b.	Phenobarbital	C_2H_5	C_6H_5
c.	Amytal	C_2H_5	$(CH_3)_2CHCH_2CH_2$
d.	Nembutal	C_2H_5	$CH_3CH_2\dot{C}H_2CHCH_3$
e.	Seconal	CH_2CHCH_2	$CH_3CH_2CH_2CHCH_3$

Figure 1. Common Barbiturates

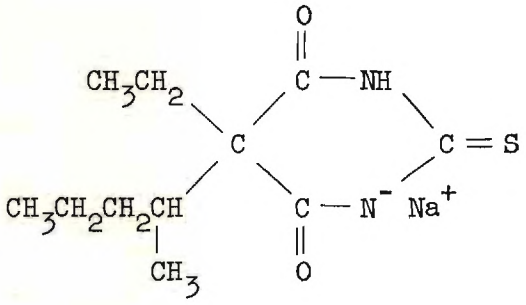


Figure 2. Pentothal Sodium

While many such compounds have been prepared and tested for physiological activity, at the time this program was undertaken, no preparation had been reported for spiro-barbituric acid derivatives in which there exists a nitrogen atom in a spiro-ring system. Previous to the syntheses of the compounds reported herein, the only nitrogen-containing spiro-barbituric acid known was "spiro-1'-benzenesulfonylpiperidine-4',5-barbituric acid" prepared by Skinner and co-workers[1] (Figure 3).

However, various other spiro systems had been investigated. The first of these reported was the spirocyclobutane-1',5-barbituric acids.

---

[1] G. S. Skinner, H. R. Krysiak, and J. A. Perregrino, J. Am. Chem. Soc., 77, 2248 (1955).

In 1921, Dox and Yoder[2] prepared a series of such compounds, formulas of which are indicated in Figure 4. A short time later these same two workers[3] reported successful syntheses of two spirocyclohexane-1',5-barbituric acids (Figure 5). Neither of these two works, however, indicated any investigation of the physiological activity of the new compounds.

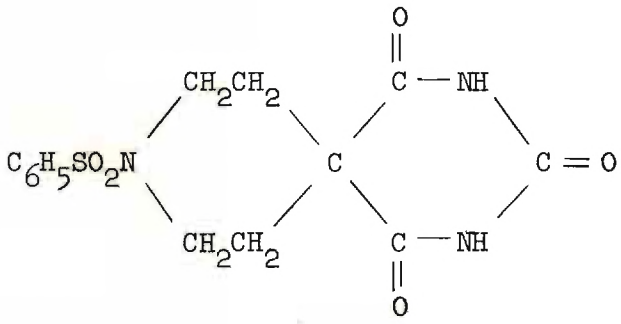
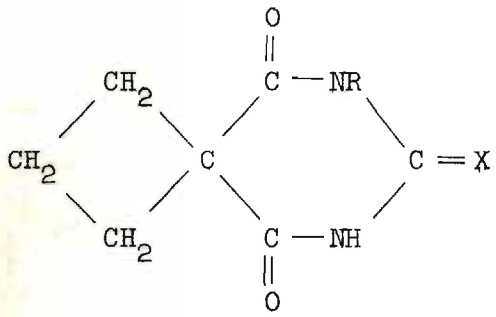


Figure 3. Spiro-1'-benzenesulfonylpiperidine-4',5-barbituric Acid



where X = NH, O, NCN or S
R = H, CH_3, C_2H_5, C_6H_5 or $C_6H_5CH_2$

Figure 4. Spirocyclobutane-1',5-barbituric Acids

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[2] A.W. Dox and L. Yoder, J. Am. Chem. Soc., 43, 677 (1921).

[3] Ibid, p. 1366.

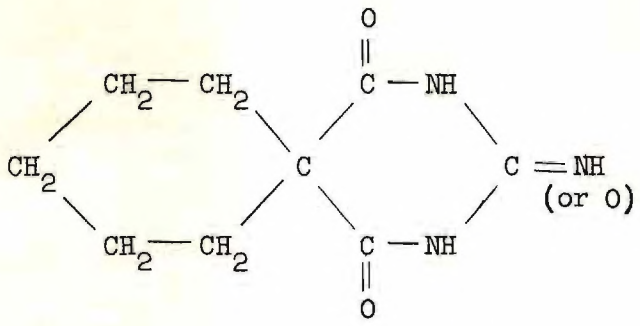


Figure 5. Spirocyclohexane-1',5-barbituric Acids

Following these two disclosures, Kamm and Waldo[4] published the preparation of an oxygen spiro system, spirotetrahydropyran-4',5-barbituric acid, "tetrahydropyran-4,5-spiro-2,4,6-triketohexahydropyrimidine" (Figure 6). This compound was tested for its physiological activity and it was found to have no hypnotic and no toxic effects when administered orally to a rabbit in dosages of 1 g. per 1.5 kg. of body weight. Barbital, for comparison, is effective in much smaller quantities, the fatal dosage to rabbits being only 0.35 g. per 1.5 kg. of body weight.

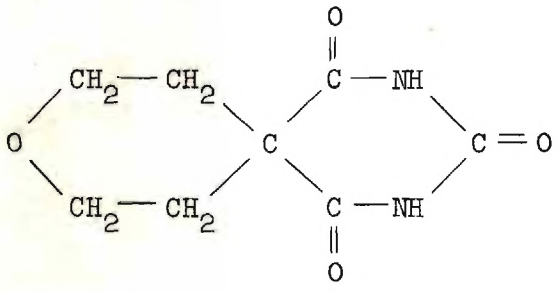


Figure 6. Spirotetrahydropyran-4',5-barbituric Acid

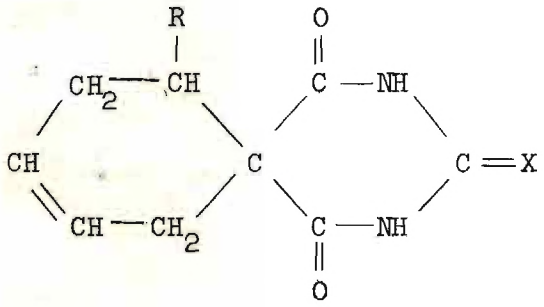
Sometime later, Cope and co-workers[5] described methods for the synthesis of spiro-barbiturates containing a six-membered carbocyclic ring.

---

[4] O. Kamm and J. H. Waldo, J. Am. Chem. Soc., 43, 2223 (1921).

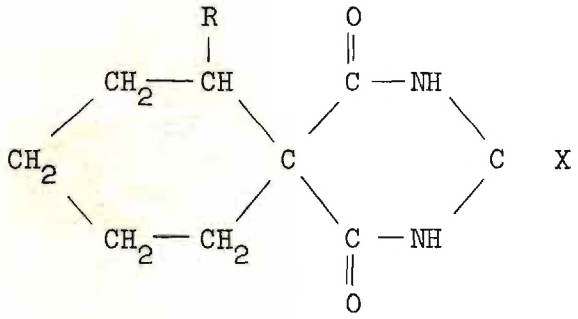
[5] A. C. Cope, P. Kovacic, and M. Burg, J. Am. Chem. Soc., 71, 3658 (1949).

These compounds, indicated in Figures 7 and 8, were similar to those of Dox and Yoder except that substitutions were made on various atoms of the molecule. However, none of these compounds was found to have unusual physiological activity; all not only were less active and longer acting, but also had poorer therapeutic ratios than barbital.



where X = O or S
R = H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, CH_3CHCH_3, or CH_3SCH_2

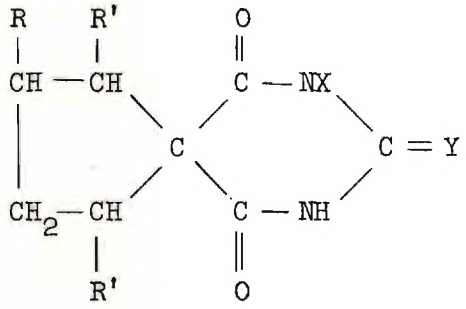
Figure 7. Spirocyclohexene-4',5-barbituric Acids



where X = O or S
R = H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, CH_3CHCH_3, or CH_3SCH_2

Figure 8. Substituted Spirocyclohexane-1',5-barbituric Acids

Doran and van Heyningen obtained two patents in 1951[6,7] for the synthesis of spiro-barbiturates involving a five-membered carbocyclic ring system (Figure 9). No report was included as to the activity of these compounds on the nervous system.



where X = Na, H, or K; Y = O or NH

R = H or CH_3; R' = CH_3 or C_2H_5

Figure 9. Substituted Spirocyclobutane-1',5-barbituric Acids

Another investigator, van Heyningen[8], has also reported a method of preparing five-and six-membered spiro-barbituric acids containing alkyl groups on the carbocyclic ring by a modified Perkin synthesis.

A later work on spiro systems was that of Giacomello and Malatesta[9] who succeeded in synthesizing spirotetrahydrothiapyran-4',5-barbituric acid (Figure 10). Again no physiological activity of the compound was indicated.

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[6] W. J. Doran and E. M. van Heyningen, U. S. Patent 2,561,688 (July 24, 1951).

[7] W. J. Doran and E. M. van Heyningen, U. S. Patent 2,561,689 (July 25, 1951).

[8] E. M. van Heyningen, J. Am. Chem. Soc., 76, 2241 (1954).

[9] G. Giacomello and P. Malatesta, Farm. sci. e. tec. (Pavia), 6, 684 (1951).

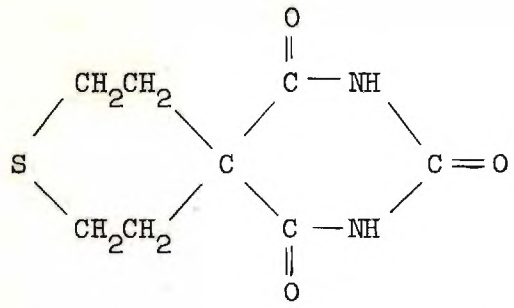

Figure 10. Spirotetrahydrothiapyran-4',5-barbituric Acid

In alkaloids the presence of a cyclic nitrogen atom is stressed in the chemistry of these materials as being a feature which sets apart these substances from other naturally occurring compounds. In the spiro-barbiturates which are reported here, there is present in the molecule a cyclic nitrogen system--the piperidine ring. The belladonna and the coca alkaloids are examples of naturally occurring materials which have, at least in part, a piperidine nucleus. Others which include this grouping are some of the hemlock alkaloids, the pomegranite alkaloids, and the areca nut alkaloids. However, the morphine alkaloids are more interesting when compared to the spiro-barbiturates containing a nitrogen atom in the spiro ring. In morphine, not only is there the piperidine nucleus (Figure 11) but also there is the non-planarity of the heterocyclic ring with the phenanthrene nucleus. In the compounds which are reported herein, there exists the piperidine nucleus together with a non-coplanar ring system--the pyrimidine ring (Figure 11).

Thus, there are several points of interest in compounds such as represented by Figure 12: first, the barbiturate ring; second, the spiro-nitrogen system or piperidine ring; and third, the non-coplanarity of the two rings involved. While each of these may have some significant effect upon the physiological activity of the whole molecule, it must be realized

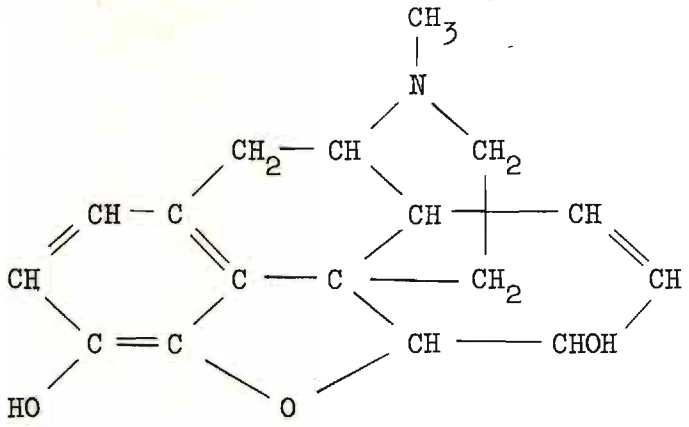

Figure 11. Morphine

one cannot make the conclusion that these compounds would possess unusual activity because of any of these points of interest. However, there does exist the distinct possibility of such compounds having physiological activity.

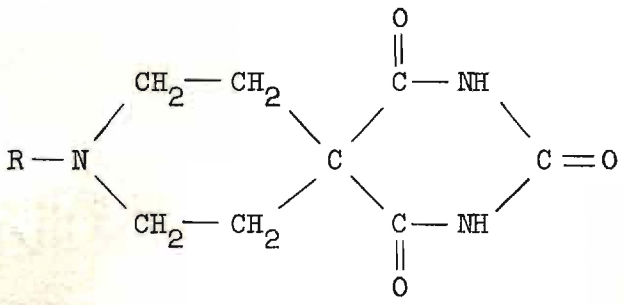

Figure 12. Spiro-amino Barbituric Acids

CHAPTER II

DISCUSSION OF EXPERIMENTAL INVESTIGATIONS

Several methods of preparing the desired spiro-amino barbituric acids were attempted. The first method involved the reaction of sodium diethyl malonate with various bis(2-haloethyl)amines. The diethyl N-alkyl piperidine-4,4-dicarboxylates which were the expected products, were to be condensed with urea, thiourea, or guanidine to yield the spiro-amino barbituric acid derivatives. An outline of the proposed reactions is diagrammed in Figure 13. The bis(2-haloethyl)amines that were needed as starting materials in reaction a (Figure 13) were prepared by the action of thionyl chloride upon the corresponding bis(2-hydroxyethyl)amine hydrochlorides. Several of these latter compounds are available commercially while many others have been previously prepared.

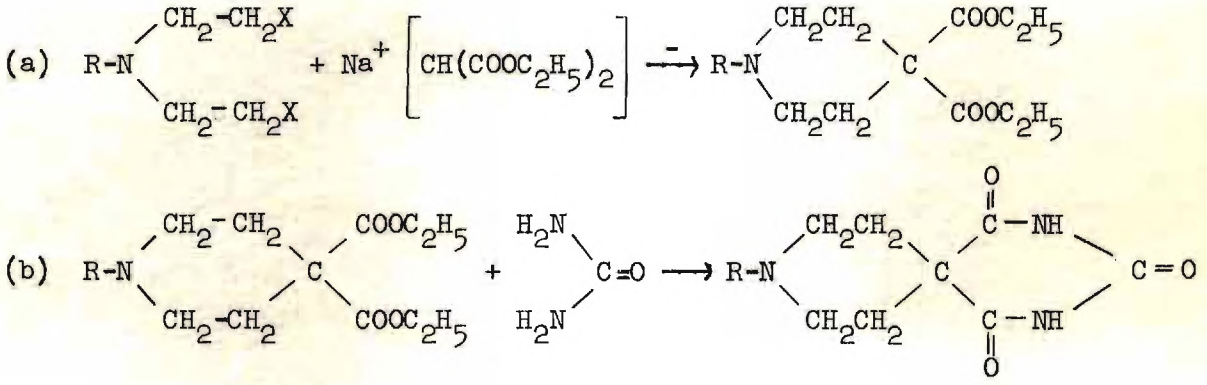

Figure 13. Equations for Procedure I

While the reaction of these nitrogen mustards with sodium diethyl malonate does not seem to have been undertaken previously, it seemed likely

that this reaction should proceed. There are similar reactions know. Thus, when β,β'-dichlorodiethyl ether is refluxed with diethyl malonate and sodium ethoxide, the oxygen analogue of the proposed compound, i.e., diethyl tetrahydropyran-4,4-dicarboxylate, is obtained.[10,11] It has also been reported that the nitrogen mustards will react with arylacetonitriles forming Demerol and similar compounds.[12] In a like manner, thiophene acetonitriles have been condensed to produce compounds containing the piperidine ring.[13] In each of these cases, sodium amide was used as the basic reagent.

It should also be mentioned in these instances branching in the carbon chains of the nitrogen mustards did not interfere with the reaction although Harnest and Burger[11] reported branching in the oxygen analogues did prevent reaction with malonic ester. Regarding this, it would appear that the report of van Heyningen,[14] in which the successful condensation of secondary alkyl halides with malonic esters was described, offers a method whereby this reaction could be made to proceed.

In the experimental work reported herein, only one attempt was made to effect condensation with urea as outlined in Procedure I and this with a compound whose identity as diethyl N-methylpiperidine-4,4-dicarboxylate was uncertain. Only a small amount of crystalline product was isolated

---

[10] G. S. Skinner, J. Am. Chem. Soc., 47, 1124 (1925).

[11] G. H. Harnest and A. Burger, J. Am. Chem. Soc., 65, 320 (1943).

[12] O. Eisleb, Ber. deut. chem. Ges., 74B, 1433 (1941); U. S. Patent 2,167,351 (July 25, 1939).

[13] F. F. Blicke, U. S. Patent 2,425,721 (August 19, 1947).

[14] E. M. van Heyningen, J. Am. Chem. Soc., 76, 2241 (1954).

from this reaction mixture. This small quantity of material was not identified and the preparation was not repeated.

The work involving the reaction shown in Procedure I was deferred because of the increased sensitivity of the experimenter to the vesicant action of the nitrogen mustards. On the basis of the incomplete experiments performed, this particular reaction scheme cannot be assumed to be ineffective; however, it was never re-examined because more satisfactory results were subsequently obtained by another reaction path.

The second method attempted involved the use of dimethyl-β-haloalkyl amines as one of the starting materials. Condensation of these with diethyl malonate in a two-step process should give rise to a disubstituted malonic ester. This substance when condensed with urea, thiourea, or guanidine should give a disubstituted barbituric acid which then could be cyclized by treatment with hydrochloric acid followed by heat. The course of these reactions is shown in Procedure II, Figure 14. An alternate plan was to effect the cyclization of the disubstituted malonic ester first and then condense the piperidine dicarboxylic ester with urea or similar compounds. This path is also indicated in Figure 14.

This method of piperidine ring formation is exemplified by the recently published synthesis of Demorol nitrile[15] and of 4,4-diphenyl-1-methyl-piperidine.[16]

The advantages of this as a possible method of synthesis of nitrogen spiro-barbiturates included the more readily available β-haloalkyl amines

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[15] F. F. Blicke, J. K. Faust, J. Krapcho, and E. Tasao, J. Am. Chem. Soc., 74, 1844 (1952).

[16] N. Sperber, M. Sherlock, and D. Pape, J. Am. Chem. Soc., 75, 1122 (1953).

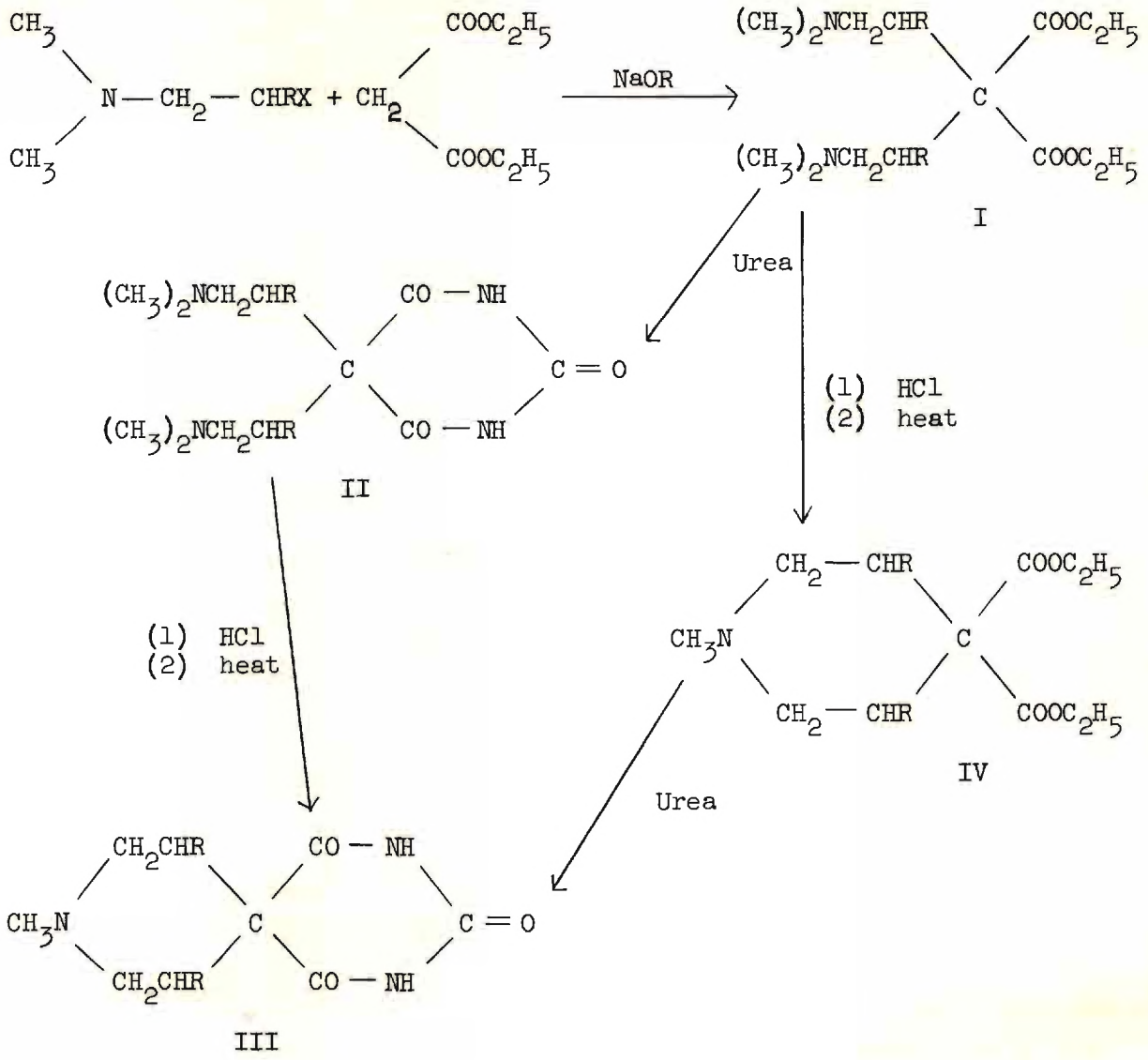

Figure 14. Equations for Procedure II

as starting materials and the less potent vesicant action exerted by these compounds as compared to the dihalodialkyl amines.

However, it was found that under the conditions employed, only one mole of the haloethyl amine could be caused to react with malonic ester conveniently. In some reactions, low yields of a liquid, thought to be the desired diester, were isolated. When this material was reacted with urea, however, no crystalline product could be obtained. Investigation of

this method (Procedure II) for preparing the spiro-amino barbituric acids was discontinued in order to concentrate effort on a more successful synthetic method. It should be noted, however, that the information obtained in these experiments would indicate that the previous reactions attempted with bis(2-haloethyl)amines might well be re-examined using the hydrochlorides of the amines and milder reaction conditions. This procedure would be advantageous since the necessity of isolating the rather unstable, and strongly vesicant, free bases would be avoided.

The successful method of preparation of spiro-amino barbituric acids utilizes spirotetrahydropyran-4',5-barbituric acid, the oxygen-containing spiro-barbituric acid prepared in 1921 by Kamm and Waldo.[17] A major advantage of this method is that the use of the vesicant 2-haloethyl amines is avoided completely. Difficulty was encountered in reproducing the yield reported by Kamm and Waldo and in several preparations, no barbituric acid was obtained. This was found to be due apparently to the very rapid rate of base-catalyzed hydrolysis of the barbituric acid ring. The product isolated in these cases was a crude tetrahydropyran-4-carboxy-4-carbonylureide containing amounts of tetrahydropyran-4-carbonylureide. More satisfactory and more consistent yields of the desired spiro compound were obtained by modifying the isolation procedure slightly.

The reaction scheme is outlined in Figure 15; included is an alternate path, which did not prove to be successful, although its possibilities were not completely explored. The cleavage of the oxygen linkage in the tetrahydropyran ring of spirotetrahydropyran-4',5-barbituric acid was accomplished by using a slight modification (larger proportions

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[17] O. Kamm and J. H. Waldo, J. Am. Chem. Soc., 43, 2223 (1921).

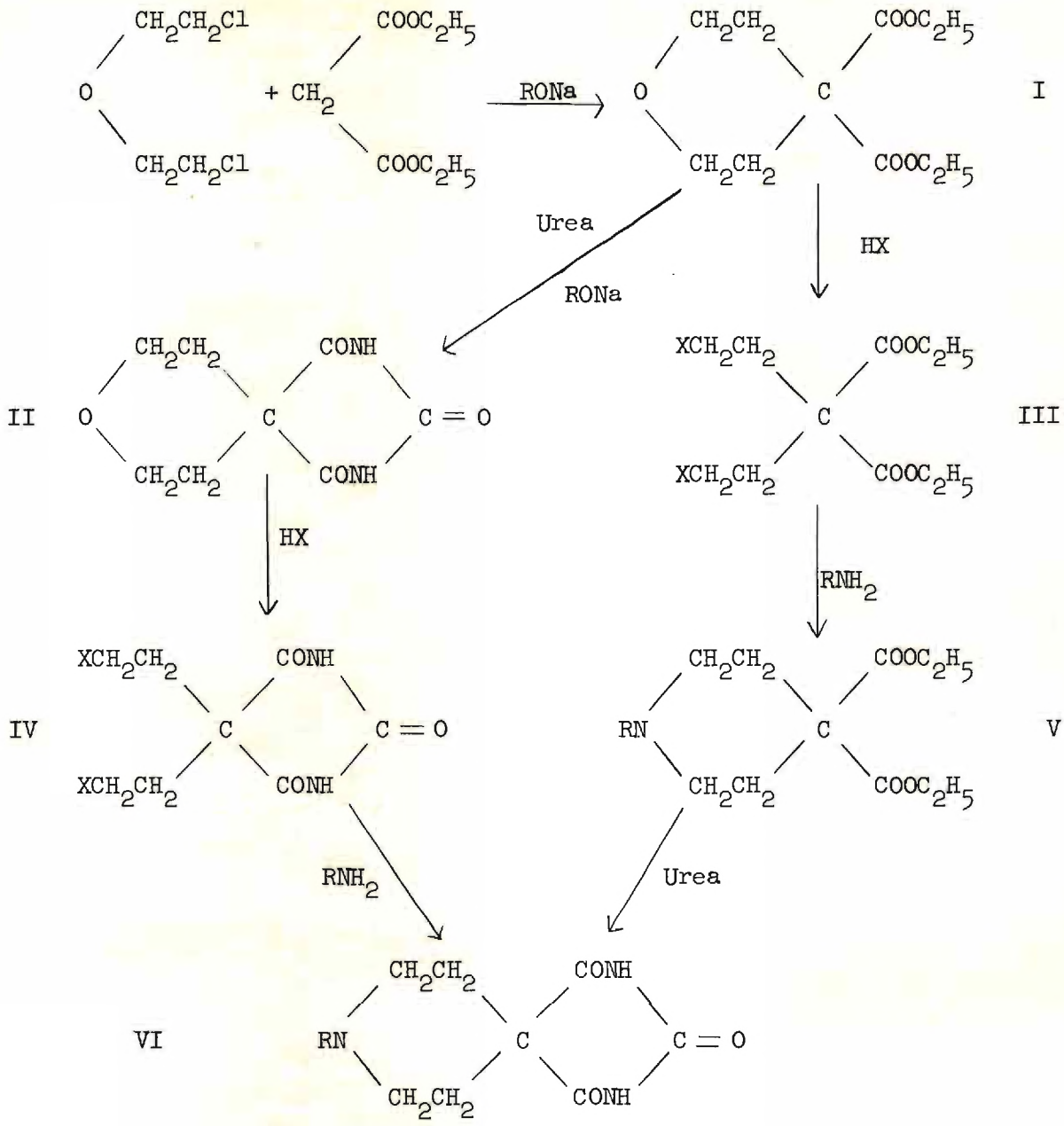

Figure 15. Equations for Procedure III

of phosphoric acid were required with the solid ether) of the method of Stone and Shechter.[18] This procedure involves the use of 95 per cent phosphoric acid and powdered potassium iodide as the source of the hydrogen

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[18] H. Stone and H. Shechter, J. Org. Chem., 15, 491 (1950).

iodide. Other attempts to effect the opening of the ether ring with hydroiodic or hydrobromic acids in water, acetic acid, or sulfuric acid were unsuccessful.

The resulting 5,5-bis(2-iodoethyl) barbituric acid was condensed with primary amines using mild reaction conditions in most cases. Using this method (Procedure III, the spiro-amino barbituric acids, as shown in Table I, have been prepared and characterized. In addition to these compounds, the previously unreported spirotetrahydropyran-4',5-thiobarbituric acid has been prepared by a procedure similar to that used to prepare the corresponding barbituric acid. Attempts to open the ether ring using the procedure that was successful with spirotetrahydropyran-4',5-barbituric acid resulted in the evolution of hydrogen sulfide and no crystalline product could be isolated from the reaction mixture.

Similarly, a compound believed to be the corresponding imino barbituric acid (spirotetrahydropyran-4',5-iminobarbituric acid) was prepared. This product, a high melting crystalline solid, was difficult to purify due to its almost complete insolubility in most common solvents. No attempt was made to cleave the ether linkage of this compound. Both the thio- and imino-barbituric acids were found to be quite unstable in aqueous basic media, the barbituric acid rings being hydrolyzed rapidly at room temperature.

The infrared spectra of the barbituric acids, intermediates, and some by-products and derivates that have been isolated were recorded using a Perkin-Elmer Model 21 double-beam recording spectrophotometer. Records were obtained of the spectra of the solid compounds from compressed potassium bromide discs (0.1 g.) containing approximately one per cent of the

Table 1. Spiro-amino Barbituric Acid

Barbituric Acid	M.P.[†]	Nitrogen	
		Calculated (%)	Found (%)
Spiro-1'-methylpiperidine'4-,5-barbituric Acid	164-166	19.89	20.07[††]
Spiro-1'-ethylpiperidine-4',5-barbituric Acid	166-167.5	18.66	18.84
Spiro-1'-(2-hydroxyethyl)piperidine-4',5-barbituric Acid	277-278	17.42	17.46
Spiro-1'-allylpiperidine-4',5-barbituric Acid	134.5-135.5	17.71	17.85
Spiro-1'-isopropylpiperidine-4',5-barbituric Acid	143-145	17.49	17.42
Spiro-1'-n-butylpiperidine-4',5-barbituric Acid	174-175	16.59	16.66
Spiro-1'-cyclohexylpiperidine-4',5-barbituric Acid	194-196	15.04	14.96
Spiro-1'-phenylpiperidine-4',5-barbituric Acid	209-210	15.38	15.18
Spiro-1'-benzylpiperidine-4',5-barbituric Acid	172.5-173.5	14.63	14.61
Spiro-1'-o-tolylpiperidine-4',5-barbituric Acid	178-179	14.63	14.30
Spiro-1'-p-tolylpiperidine-4',5-barbituric Acid	157-158	14.63	14.68
Spiro-1'-(2-phenylethyl)piperidine-4',5-barbituric Acid	165-167	13.94	13.75

[†]Unless otherwise noted all melting points are in degrees centigrade and were determined using a Kofler hot-stage micro melting point apparatus, and, therefore, are corrected. The melting of the amino-barbituric acids is accompanied with decomposition and the melting point varies slightly with the rate of heating.

[††]Calculated for $C_9H_{13}N_3O_3$: C = 51.18 per cent; H = 6.20 per cent
Found: C = 51.45 per cent; H = 6.19 per cent

compound. The reference beam intensity was adjusted by inserting fine wire screens between the source and the detector. Examination of the spectra of the liquids was made using samples contained in a 0.022 mm. cell without a solvent. These infrared spectra are reproduced in the Appendix.

In general the infrared curves of the spiro-amino barbituric acids exhibit a strong doublet at 5.80 to 5.85 and 6.00 ± 0.05 microns. In spiro-1'-(2-hydroxyethyl)piperidine-4',5-barbituric acid this doublet is shifted slightly towards higher wavelengths, appearing at 6.10 and 6.22 microns. In spiro-1'-allylpiperidine-4',5-barbituric acid the two absorption bands appear at 5.85 and 5.92 microns. Thus, with the exception of spiro-1'-methylpiperidine-4',5-barbituric acid, which exhibits a single broad absorption band in this region, all the spiro-aminobarbituric acids have a doublet in the region of 6 microns. It is, therefore, suggested that the absorption band of lower wavelength be assigned to the C = O stretching and the second absorption band be assigned to the C = N stretching band, with the presence of the C = N stretching band being indicative of an inner salt structure for the spiro-amino barbituric acids. This indication of zwitterionic character is further substantiated by absorption in the ultraviolet region of the spectrum.

The presence of many distinct bands in the spiro-amino barbituric acids between 6 and 7 microns (none of which are present in other barbituric acids, but which do appear in the spectra of sodium salts of barbituric acids[19]) further points to a salt-like structure.

In the spectra of spirotetrahydropyran-4',5-thiobarbituric acid, the carbonyl absorption appears as a distinct doublet at 5.75 and 5.90 microns.

[19] L. Levi, and C. E. Hukley, Perkin-Elmer Instrument News, 5, No. 2, 1 (1954).

The carbonyl absorption in the corresponding barbituric acid occurs as a single broad band from about 5.85 to 5.90 microns. In addition, the thiobarbituric acid showed absorption bands at 6.55 and 8.6 microns, which absorptions have been previously assigned to thiobarbiturates.

The absorption bands appearing at 10.1 and 10.8 microns in spiro-1'-allylpiperidine-4',5-barbituric acid is in agreement with the assignment of such bands to allyl substitution in 5,5-dialkyl barbituric acids. This pair of absorption bands does not appear in the spectra of the other barbituric acids examined.

With the exception of a broad absorption band near 12 microns, which was found in the spectra of most of the barbituric acids examined, and the out-of-plane hydrogen bending bands present in the spectra of those barbituric acids having an aromatic substituent, no further absorption band assignments were made.

Some observations (using a Beckman DK-2 recording spectrophotometer) have been made in the ultraviolet region on aqueous solutions of spirocyclopentane-1',5-barbituric acid, spirocyclohexane-1',5-barbituric acid, spirotetrahydropyran-4',5-barbituric acid, spiro-1'-methylpiperidine-4',5-barbituric acid, and on basic aqueous solutions of these four materials. The absorption spectra in this region is compared to that of 5,5-dialkyl-barbituric acids in Table 2. None of these compounds absorbed in the region 220 to 340 mμ as the free acids (i.e., in deionized water or in a Coleman buffer of pH = 7.0). An exception was the spiro-amino barbituric acid. This compound absorbed strongly at 262 mμ in water (deionized) or a pH = 7 buffer. In strongly acid solution, 1.057 N or 10.5 N HCl, this compound exhibited an absorption band at 230 mμ.

Table 2. Absorption of Barbituric Acids (220-340 mμ)

Barbituric Acid	Wavelength in mμ Maximum Absorption in a Solution of pH 7.0	pH 9.9	0.8 M NaOH	4.5 M NaOH
5,5-dialkyl-[†]	none	240	255	255
spirocyclopentane-1',5-	none	242	232	---
spirocyclohexane-1',5-	none	242	232	---
spirotethydropyran-4',5-	none	242	232	230
spiro-1'-methylpiperidine-4',5-	262[††]	262	244	245

[†] T. C. Butler, J. M. Ruth, and G. F. Tucker, Jr., J. Am. Chem. Soc., 77, 1486 (1955).

[††] In deionized water or in a buffered solution.

The 5,5-diethylbarbituric acid and various 5,5-dialkylbarbituric acids have an absorption maximum at 240 mμ in a solution of pH = 9.9. In this solution these compounds reportedly exist as monovalent anions. They exhibit a maximum absorption in strongly basic solutions (4.5 molar sodium-hydroxide) at about 255 mμ; this absorption is assigned to the divalent species. As a rough analogy to α-β-unsaturated diketones these absorptions would be within the limits predicted by Woodward's rules.[20] For example, Woodward's rules[20] indicate that a ketone such as $R - \overset{O}{\overset{\|}{C}} - \overset{H}{\overset{|}{C}} = CR_2$ would have a maximum absorption at 239 ± 5 mμ. The structure, $\underbrace{\overset{O}{\overset{\|}{C}} - NH - \overset{O}{\overset{\|}{C}} - N = \overset{O^-}{\overset{|}{C}} - CR_2}$, which is similar has a maximum absorption at 240 mμ. The production of a more highly conjugated system on going to the divalent ion would be expected to absorb nearer the visible, as in the case with 5,5-dialkylbarbituric acids.

[20] R. B. Woodward, J. Am. Chem. Soc., 63, 1123 (1941).

Ignoring for the present the spiro-1'-methylpiperidine-4',5-barbituric acid, all the spiro-barbituric acids have been found to absorb in a buffer solution of pH = 9.9 at 242 mμ. This again is in agreement with the analogy made to α-β-unsaturated diketones. However, on going to a more basic solution, the absorption maximum for the spiro compounds was found to be at about 232 mμ, a shift of absorption away from the visible.

The spiro-amino barbituric acid in neutral or pH = 9.9 solution was found to absorb at 262 mμ with a shift in the absorption maximum to 244 mμ upon going to strongly basic solution (0.8 N NaOH or 4.5 N NaOH). This shift in absorption away from the visible upon going from weakly basic to strongly basic solutions then appears to be characteristic of those barbituric acids containing a spiro carbon atom.

Further, it has been observed that spirotetrahydropyran-4',5-thiobarbituric acid (although in the ultraviolet region this compound has a rather complex absorption), also exhibits a shift of absorption away from the visible upon going from weakly basic to strongly basic solutions (i.e., two peaks at about 300 and 260 mμ in a pH = 9.9 to two peaks at about 278 and 234 mμ in sodium hydroxide solutions.)

A structure such as indicated in Figure 16 might be suggested for the divalent ions formed with spiro type compounds. An explanation might be that there is sufficient strain, introduced by the spiro structure, to prevent the formation of a longer conjugation such as could exist when the 5,5-dialkylbarbituric acids are converted to divalent ions (see Figure 17). The structure proposed for the spiro divalent ions would not be sufficiently different from that of the monovalent ions insofar as the

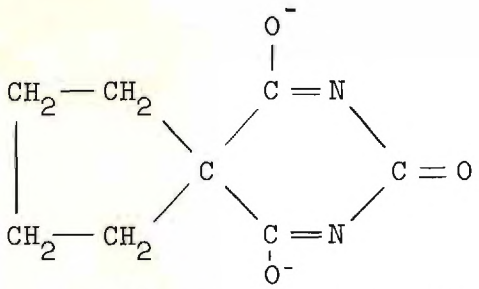

Figure 16. Proposed Structure for Spiro Divalent Ion

ultraviolet absorption is concerned, to effect much change in the absorption maximum. It should be noted that the maximum absorption for the spiro divalent ions occurs at 232 mμ. This value is not far from 239 ± 5 mμ which would be predicted by the α,β-unsaturated ketone analogy.

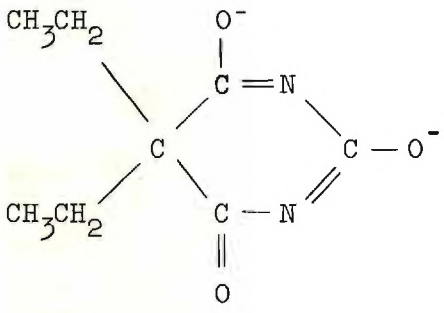

Figure 17. Divalent Dialkylbarbituric Acid Anion

In basic solutions the intensity of these absorption bands decrease with time. This decrease, which is due to the disappearance of the barbituric acid structure was used then to follow the rate of basic hydrolysis.

Since the absorptions are due to conjugation in the ionic form of the barbituric acid derivations and since the hydrolysis products do not absorb within the wavelength range under consideration, the optical densities would be essentially zero at infinite time. This has been shown to be true by allowing basic solutions of spirocyclohexane-1',5-barbituric acid, spirocyclopentane-1',5-barbituric acid, and spirotetrahydropyran-4',5-barbituric acid to stand for prolonged periods of time and then

determining the optical density of the resulting solution of the hydrolysis products. In addition, it has been shown that a 10^{-4} molar solution of tetrahydropyran-4-carbonylureide, one of the products of the hydrolysis of spirotetrahydropyran-4',5-barbituric acid, does not absorb in the region 220-340 mμ.

During a hydrolysis then, the optical density would fall from some maximum value to zero and a plot of the optical density values versus time would give a curve description of the reaction rate and order. If the base is kept constant (by means of a large excess or by means of a buffer solution) the curve obtained would be descriptive of the dependance upon concentration of the barbituric acid.

Using conditions where the barbituric acids existed as divalent ions and where the hydroxide ion concentration was essentially constant throughout the reaction, pseudo-first-order rate curves were obtained, showing first-order dependence upon the concentration of the barbituric acids. From this type of data a comparison of the relative stabilities of the spiro-barbituric acids could also be made. These data are given in Table 3. As a reference compound, 5,5-diethylbarbituric acid was hydrolyzed under essentially the same conditions and its hydrolysis rate data are included in Table 3 with the spiro-barbituric acids which have been run.

It is readily apparent from the half life values that the spirocyclopentane-1',5-barbituric acid undergoes hydrolysis 928 times as rapidly as the model compound, 5,5-diethylbarbituric acid, with the strongly basic conditions used. The spirotetrahydropyran-4',5-barbituric acid hydrolyzed 346 times as fast as the model compound and the spirocyclohexane-1',5-barbituric acid 252 times as fast.

Table 3. Hydrolysis Data

Barbituric Acid	Acid Con.	NaOH Con.	Temp. °C.	k'_{-1} Min.	$t_{1/2}$ Min.	Wave-length mμ
5,5-diethyl	10^{-4}M	0.9505N	40.2	6.22×10^{-4}	1114	253
Spirocyclopentane-1',5-	10^{-4}M	0.9505N	40.0	0.576	1.20	232
Spirocyclohexane-1',5	10^{-4}M	0.9505N	40.0	0.157	4.43	232
Spirotetrahydropyran-4',5-	10^{-4}M	0.9505N	40.0	0.215	3.22	232
Spiro-1'-methyl-piperidine-4',5-	10^{-4}M	0.9505N	40.2	5.35×10^{-4}	1295	244

In contrast to the other spiro-barbituric acids, the spiro-1'-methylpiperidine-4',5-barbituric acid hydrolyzes at a slightly slower rate than does the model compound.

In order to obtain data concerning the effect of temperatures upon the hydrolysis rate of spiro-barbituric acids, runs were made using solutions 0.9272 normal in sodium hydroxide and 10^{-4} molar in spirotetrahydropyran-4',5-barbituric acid. Only two temperatures were used, 30 and 40° C. The data obtained presented in Table 4 indicated that the pseudo-first-order hydrolysis constants were 0.102 and 0.189 reciprocal minutes at 30 and 40° C. respectively. Based upon the rates at these two temperatures, the apparent Arrhenius activation energy was calculated to be approximately 11.6 kilo-calories.

Upon changing the concentration of the base to 0.0905 normal a marked change in the absorption maximum resulted. This shift would mean

Table 4. Temperature Effect on
Hydrolysis of Spirotetrahydropyran-4',5-barbituric Acid

Acid Con.	Base Con.	Temp. °C.	k' Min.$^{-1}$	Half Life Min.
10^{-4}	0.8272	30	0.102	6.79
10^{-4}	0.8272	40	0.189	3.67

an appreciable quantity of the monovalent species was now present in the reaction mixture. Under such conditions a measure of the decrease in the absorption maximum with time would be a measure of the combined rates of disappearance of two different ionic species. Such a determination would have no significance; therefore, no rate data were collected.

At 40° C. the hydrolysis rate (measured at 232 mμ) of 10^{-4} molar solutions of spirotetrahydropyran-4',5-barbituric acid changed with comparatively small variations in total sodium hydroxide concentration. These data are given in Table 5.

Table 5. Effect of Base Concentration on Hydrolysis Rate

Acid Con. (Molar)	Base Con. (Normal)	Temp. °C.	k' Min.$^{-1}$	Half Life Min.
10^{-4}	0.4136	40	0.176	3.94
10^{-4}	0.8272	40	0.189	3.65
10^{-4}	0.9505	40	0.215	3.22

These preliminary data serve only to indicate a dependence upon hydroxide ion concentration in these hydrolyses.

In contrast to the rapid rate of hydrolysis of spirocyclopentane-1',-5-barbituric acid in the strongly basic medium, the rate at 40° C. in a

buffer solution having a pH of 9.9 was found to be considerably slower. The apparent pseudo-first-order reaction rate constant was found to be 1.07 x 10^{-2} reciprocal minutes, or, the reaction is half complete in 65 minutes as compared to only 1.2 minutes at the higher base strength.

At the lower pH value the absorption measurements were made at 240 mμ. It was, then, the disappearance of the monovalent ion species which was measured. The moderate rate with which this compound undergoes hydrolysis in a solution where it exists essentially as a monovalent ion makes it apparent that such conditions would be more convenient for measuring the hydrolysis rates.

The mechanism of these hydrolysis is probably similar to the base catalyzed solvolysis of β-diketones, 2-ketoalkylpyridinium salts, and chloral hydrate.[21]

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[21] R. G. Pearson, et al., J. Am. Chem. Soc., 70, 1933 (1948); J. Am. Chem. Soc., 73, 926, 931 (1951).

CHAPTER III

EXPERIMENTAL

All boiling points recorded herein are uncorrected. The melting points designated as (unc) are uncorrected and were determined in capillary tubes heated in an aluminum block. The melting points designated (K) were determined using a Kofler hot-stage micro melting point apparatus and are, therefore, corrected. Analysis for carbon, hydrogen, and nitrogen were performed by either Clark Microanalytical Laboratory, Urbana, Illinois or Geller Laboratories, West Engelwood, New Jersey.

Syntheses with Bis(2-haloethyl)amines

Introduction.--The experiments reported herein are those initial attempts with the nitrogen mustards which were later deferred. This particular reaction scheme, outlined in Figure 13, cannot be assumed to be ineffective on the basis of these few incomplete experiments. However, this reaction path has not been re-examined because of the more promising results obtained by other methods.

Purification of Thionyl Chloride.--Practical grade thionyl chloride (1000 g.) was refluxed (in all-glass apparatus) for six hours with 25 g. of flowers of sulfur and then distilled from the sulfur through a short fractionating column. Fractionation through a more efficient column yielded about 40 g. of sulfur monochloride (yellow forerun) and 880 g. of very pale yellow constant boiling thionyl chloride.[22]

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[22] D. L. Cottle, J. Am. Chem. Soc., 68, 1381 (1946).

Preparation of Bis(2-chloroethyl)methylamine Hydrochloride.--The procedure was adopted from the method of Ulrich, Ploetz, and Bogemann.[23] Methyldiethanolamine (119 g.; 1 mole) was dissolved in 125 ml. of dry chloroform in a three-necked, round-bottomed liter flask fitted with a condenser equipped with a calcium chloride drying tube. Dry hydrogen chloride gas was introduced into the solution until there was an increase in weight equal to one mole, 36.5 g. During the addition the flask was cooled when necessary by means of an ice-water bath. After the gas source was removed, a separatory funnel containing 272 g. (2.5 moles) of purified thionyl chloride dissolved in 125 ml. of dry chloroform was inserted into the reaction flask. The thionyl chloride solution was allowed to drip into the stirred suspension of the amino-alcohol hydrochloride at 50° C. at such a rate that the reaction proceeded vigorously. At the completion of the addition, the mixture was heated at 65° C. for about an hour to complete the reaction. (Evidence of this was no further evolution of hydrogen chloride and sulfur dioxide.) The condenser was arranged for distillation and the volatile products, excess thionyl chloride, and chloroform were removed by means of reduced pressure distillation. The orange colored residue was recrystallized from dry acetone as white leaflets which melted at 110-112° C. (unc) and weighed 175 g. (91 per cent).

Preparation of Bis(2-chloroethyl)methylamine.--A solution of 80 g. (0.415 mole) of the hydrochloride of bis(2-chloroethyl)methylamine was dissolved in 100 ml. of cold water and cooled in an ice-water bath. Excess 20 per

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[23] H. Ulrich, E. Ploetz, and M. Bogemann, U. S. Patent 2,163, 181 (June 20, 1939).

cent sodium hydroxide solution was added slowly enough to maintain the temperature below 25° C. The free base that separated as an oil was extracted with several 50-ml. portions of benzene and the extract dried over sodium hydroxide for an hour. Following removal of the benzene by distillation at reduced pressure, the oil was distilled. Fifty-two g. of colorless product distilling at 60-70° C. under 2-4 mm. pressure was obtained. This represented an 80 per cent conversion from the hydrochloride.

Another 72 g. portion (0.374 mole) of the hydrochloride was treated similarly and yielded in 26 g. of base. This low yield (45 per cent) was probably due to incomplete extraction.

Diethyl N-Methylpiperidine-4,4-dicarboxylate.--A procedure similar to that used for the preparation of diethyl tetrahydropyran-4,4-dicarboxylate was employed.[24]

To a solution of 11.5 g. (0.5 g. at.) of sodium dissolved in 200 ml. of absolute ethanol in a three-necked, round-bottomed liter flask, fitted with a stainless steel stirrer, a dropping funnel, and a reflux condenser was added 80.1 g. (0.5 mole) of diethyl malonate. After the mixture had been stirred for a short time, 52 g. (0.33 mole) of methyl-bis(2-chloroethyl)amine was added and the mixture refluxed overnight with stirring. (Sodium chloride began to precipitate almost at once after the addition of the amine, and heat was evolved.) Another 11.5 g. of sodium dissolved in 200 ml. of absolute ethanol was added followed by an additional 26 g. (0.167 mole) of the amine. The refluxing was continued for 20 hours at which time the stirring was stopped, the sodium chloride

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[24] G. H. Harnest and A. Burger, J. Am. Chem. Soc., 65, 370 (1943).

allowed to settle out, and the liquid portion decanted through a filter. Distillation removed the alcohol and the remaining amber colored liquid was treated with 50 ml. of cold water and extracted three times with 50-ml. portions of ether. The ether extracts were combined, dried briefly with sodium hydroxide pellets, and the ether removed by distillation. The remaining oil was fractionated at 10 mm. pressure. The fraction boiling at 96 - 156° C. was collected and refractionated at 607 mm. pressure. The portion distilling at 115-133° C. (mainly at 128-133° C.) weighed 7.5 g., a yield of only 6.3 per cent of the theoretical.

This pale yellow product gave a positive test for esters, a positive nitrogen test, and evolved a basic gas when fused with sodium. An attempt to isolate a solid hydrochloride by passing hydrogen chloride into a benzene solution of the oil was unsuccessful. However, this product was assumed to be the expected diester and was used in the next preparation.

Attempted Preparation of Spiro-1'-methylpiperidine-4',5-barbituric Acid.--To 1.36 g. (0.059 g. at.) of sodium dissolved in 100 ml. of dry isopropyl alcohol in a 200-ml. round-bottomed flask were added 7.2 g. (0.030 mole) of the supposed diethyl N-methylpiperidine-4,4-dicarboxylate and 3.54 g. (0.059 mole) of urea. The resulting mixture was refluxed for 40 hours after which time practically all the alcohol was removed by means of distillation at reduced pressure. The remaining salts were washed from the flask with absolute ether, filtered, and divided into two equal portions.

One part was dissolved in five ml. of cold water and treated with a slight excess of concentrated hydrochloric acid. Since no precipitate had formed after the solution stood for several days in the refrigerator, attempts were made to extract the solution with ether. Nothing could be

extracted either from the slightly acid solution or from the solution when it was made slightly basic with ammonium hydroxide. The solution was made neutral to litmus and returned to the refrigerator. After it had stood for several more days crystals appeared. Although they darkened when heated in a Bunsen burner flame, they did not melt and appeared mainly inorganic.

The other portion was placed in about 15 ml. of dry ethanol, and an excess of ethanolic hydrogen chloride solution was added. The solid which precipitated was separated by filtering. In a preliminary test it appeared that the amino-acid hydrochloride was soluble to some extent in hot isopropyl alcohol and hence extraction with this solvent should serve to separate the organic salt from the sodium chloride. (This separation was tried on a small portion of the salts, and although the substance which precipitated when the alcohol was cooled was not immediately isolated, the method seemed to be feasible.) Consequently, a continuous extraction was attempted but, unfortunately, the isopropyl alcohol evaporated to dryness due to a leak in the apparatus and the organic material from the reaction was decomposed.

The small amount of crystalline material from the preliminary separation was then isolated and recrystallized from a small quantity of absolute alcohol containing several drops of water. The tan powdery solid melted at approximately 210-215° C. (unc) with decomposition. The melting point could not be determined exactly as the material darkened considerably at about 205° C. The total sample was used for this one determination.

This reaction was not repeated since it was necessary to suspend work due to increased sensitivity of the experimenter to the vesicant action of the mustards.

The condensation procedure used in the above preparation is similar to that of Cope, Kovacic, and Burg.[25]

Attempted Preparation of Bis(2-chloroethyl)phenylamine.--Dry hydrogen chloride was passed into a chloroform (300 ml.) suspension of 181 g. (1 mole) of phenyldiethanolamine in a three-necked, round-bottomed liter flask fitted with a condenser and stirrer, until no more appeared to be absorbed. Heat was evolved and there resulted an amber colored solution to which was added 236 g. (2.3 moles) of thionyl chloride dissolved in 200 ml. of dry chloroform. The addition was controlled so that a rapid evolution of hydrogen chloride and sulfur dioxide was maintained and the temperature was held at 60-65° C. In order to complete the reaction, the mixture was kept at this temperature for about an hour after all the thionyl chloride had been added. The chloroform and excess thionyl chloride were removed by means of distillation at reduced pressure. There remained a thick, dark red oil that should have been the expected amine. However, when purification by distillation at reduced pressure was attempted, rapid decomposition took place and no product was isolated. The distillation of this base at 164° C. under a pressure of 14 mm. had been reported.[26]

Preparation of Bis(2-chloroethyl)amine Hydrochloride.--The procedures were adopted from the methods of Ulrich, et al.[27]

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[25]A. C. Cope, P. Kovacic, and M. Burg, J. Am. Chem. Soc., 71, 3658 (1949).

[26]R. Robinson and J. S. Watt, J. Chem. Soc., 1934, 1536.

[27]H. Ulrich, E. Ploetz, and M. Bogemann, U. S. Patent 2,163,181 (June 20, 1939).

Dry hydrogen chloride gas was passed into 200 g. (1.9 moles) of diethanolamine contained in a two-liter beaker until there was a gain in weight equal to 1.9 moles of the gas. About 400 ml. of dry chloroform was added and the mixture was stirred while 500 g. (4.2 moles) of technical grade thionyl chloride was added. The addition was regulated so the reaction proceeded vigorously and the temperature was maintained at about 40-50° C. The stirring became difficult during the addition due to the formation of a sticky mass, but as the remainder of the thionyl chloride was added, the mixture again became an oil. When all the thionyl chloride had been added, an additional 400 ml. of dry chloroform was introduced and the temperature maintained at 45-50° C. for about one hour, at which time the hydrochloride of bis(2-chloroethyl)amine solidified. The pale yellow crystalline product was filtered with suction and washed twice with dry chloroform and twice with dry ether. There resulted 311 g. of white leaflets melting at 208-210° C. (unc). This weight amounted to 87 per cent of the theoretical yield.

Preparation of this compound without the use of a solvent resulted in an 80 per cent yield of impure product melting over a range of 175-190° C. (unc).

Preparation of Bis(2-chloroethyl)amine.--A solution of 300 g. of the hydrochloride of bis(2-chloroethyl)amine in 150 ml. of cold water was made basic by slowly adding (while cooling) an excess of 40 per cent sodium hydroxide solution. The base which separated as a dense oil was reddish in color and weighed 186 g., a conversion of 77.5 per cent from the salt. It was used at once, since it appeared to decompose upon standing.

Attempts to isolate the base from the chloroform suspension of the hydrochloride by adding sodium hydroxide solution, separating the base-containing chloroform layer, and drying and distilling at normal pressures were unsuccessful. Violent decomposition occurred just after the temperature rose to about the boiling point of chloroform.

Attempted Preparation of Diethyl Piperidine-4,4-dicarboxylate.--The method used is similar to the preparation of diethyl N-methylpiperidine-4,4-dicarboxylate.

Two-hundred-four g. (1.28 moles) of diethyl malonate was added to 24.5 g. (1.5 g. at.) of sodium dissolved in 300 ml. of absolute ethanol in a three-necked, round-bottomed liter flask equipped with a stainless steel stirrer, dropping funnel, and reflux condenser. After the mixture had been stirred for several minutes, 180 g. (1.28 moles) of bis(2-chloroethyl)amine was added. Immediately the reaction mixture became quite thick and could not be stirred efficiently. Since no further change was noted after heating for two hours, an additional 23.9 g. (1.04 g. at.) of sodium in 300 ml. of absolute ethanol was added and the reaction mixture refluxed with stirring for 48 hours. After standing for several days, the thick emulsion was centrifuged and a waxy yellow substance was partially removed. The alcohol was separated from the cloudy yellow liquid by distillation and the remaining paste treated with cold water and extracted with three 100-ml. portions of ether. The extract was dried and the ether removed by distillation. Fractionation of the resulting oil yielded nothing but unreacted diethyl malonate.

All attempts to isolate any pure product from the waxy substance were unsuccessful.

Syntheses with Dimethylaminoethylchloride

Introduction.--The reactions described on the following pages were run to determine if condensations of dimethylaminoethylchloride with diethyl malonate were feasible. (Refer to Figure 14 in Chapter II.) They also served to demonstrate that relatively mild temperatures were advantageous.

It was thought that the resulting amino esters, I, would be condensed with urea or thiourea to produce amino barbiturates, II. It should also be possible to eliminate trimethylamine from the disubstituted barbituric acid, II, or the disubstituted ester, I, to produce either the desired spiro-amino barbiturate, III, or an ester, IV, capable of being converted into the spiro-amino barbiturate, III.

The information obtained from the condensation reactions indicated that previous reactions attempted with bis(2-haloethyl)amines might well be tried again using the hydrochloride of the amine and milder reaction conditions. This procedure would be advantageous since the necessity of isolating the rather unstable, and the strongly vesicant, free bases would be avoided.

It should be noted, however, that although the first condensation of the 2-haloethylamine hydrochloride with malonic ester went quite readily, it was not feasible, employing rather mild reaction conditions, to introduce a second fragment.

Preparation of Dimethylaminoethyl Chloride Hydrochloride.--This preparation was based upon the method described by Ulrich, et al.[28]

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[28] H. Ulrich, E. Ploetz, and M. Bogemann, U. S. Patent 2,163,181 (June 20, 1939).

Dry hydrogen chloride was passed into a solution of 217 g. (2.5 moles) of dimethylethanol amine in 200 ml. of chloroform, cooled to 5° C., until there was a gain in weight of 92 g. (approximately 2.5 moles of hydrogen chloride). This mixture was allowed to stand at room temperature overnight.

Practical grade thionyl chloride (375 g. 229 ml.) was added to the amino alcohol hydrochloride solution at 40-50° C. The first 50 ml. were added as a solution in 50 ml. of chloroform, the remainder being added without solvent. The addition required 30 minutes. The resulting mixture was stirred at 40° C. for about two hours until evolution of gas ceased. When crystallization of the product took place, sufficient additional chloroform (unmeasured) was added to allow efficient stirring.

The mixture was cooled and filtered with suction, pressing the solid firmly upon the filter to aid in removing the solvent. The product was washed on the filter twice with cold chloroform, then once by stirring to a thin paste with cold chloroform and refiltering. The white crystalline solid was transferred to a vacuum dessicator and the residual solvent was removed using reduced pressure. The resulting 310 g. (87.5 per cent of the theoretical yield) had a slight odor resembling thionyl chloride and melted at 203.5-205° C. (unc). The hydrochloride is reported in the literature to melt at 201° C.[29]

Diethyl 2-dimethylaminoethylmalonate.--A solution of sodium ethoxide (5.2 g. of sodium: 0.236 g. at.) in 150 ml. of absolute ethanol was added to a suspension of 14.4 g., 0.1 mole, of dimethylaminoethyl chloride hydrochloride in 100 ml. of absolute ethanol containing 37.8 g. (0.118 mole) of

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[29] K. H. Stotta, and R. Behnisch, Ber. deut. Chem. Ges., 68B, 754 (1935).

diethyl malonate. The addition was made over a 15-minute period and there was only a mild evolution of heat. After stirring at room temperature for 20 hours, the alcohol was removed by distilling until the temperature of the distillate reached 100° C. The residue was cooled, treated with cold water to dissolve the salt, and extracted five times with 75-ml. portions of ether. Drying, then removing the solvent at reduced pressure yielded an oil that was distilled without fractionation at a pressure of 6 mm. Practically all the material passed over between 81° and 125° C. This material, product A, was fractionated through a Todd column rated at 60 plates. The results are shown in Table 6. Assuming fractions 2, 3, and 4 to be the product, the yield was 12 g. or 52 per cent of the theoretical amount.

Table 6. Fractionation of Product A

Fraction	Pressure (mm. Hg)	Temperature (° C.)	Weight (g.)	Refractive Index (25° C.)
1	6-7	to 100 (Mainly 68-73)	15	1.41264†
2	3	101-102	3	1.43093
3	3.5	104.5-105	4	1.43089
4	3.5	105	5	1.43086

†Unreacted malonic ester. Handbook gives $N_D^{20} = 1.4143$.

Upon shaking the compound with concentrated ammonium hydroxide for two hours and evaporating the base and water (aspirator pressure and warm water bath) there resulted a solid, presumably the diamide, which, after one recrystallization from ethanol, darkened at 174.5° C. and melted at 177° C. (unc).

The compound formed a solid hygroscopic hydrochloride upon being treated with gaseous hydrogen chloride. This salt was never isolated in a pure state. The compound yielded a solid picrate which did not melt below 360° C. after one recrystallization from ethanol.

Another preparation of diethyl 2-dimethylaminoethylmalonate was made using 0.5 mole of dimethylaminoethylchloride hydrochloride. Ethanolic sodium ethoxide (0.5 mole) was used to neutralize the mineral acid portion of the salt prior to adding 96 g. of malonic ester (0.6 mole). An additional 0.5 mole of ethanolic sodium ethoxide was added over a 15-minute period. The mixture was stirred for 20 hours at room temperature, after which the alcohol was removed using aspirator pressure and a hot water bath. The residue was treated with 100 ml. of ether and enough cold water to dissolve the salt. The layers were separated and the aqueous portion further extracted with five 60-ml. portions of ether. After drying the extract with $CaSO_4$ and removing the ether, fractionation of the product, B, gave the materials shown in Table 7.

Fraction 6 was collected over an eight-hour period and probably represents a pure compound. The yield of product, fractions 4 through 8, was 39.9 g. or 34.8 per cent.

A small sample of the amine ester was treated with excess methyl iodide. The methiodide, after recrystallizing from ethanol-ethylacetate, melted at 122-123.5° C. (unc).

Calculated for $C_{12}H_{24}NO_4I$: I = 34.0 per cent

Volhard method: I = 34.2 per cent

Diethyl Bis(2-dimethylaminoethyl)malonate.--Dimethylaminoethyl chloride hydrochloride (28.8 g.: 0.2 mole) was suspended in a solution of 32 g.

Table 7. Fractionation of Product B

Fraction	Pressure (mm. Hg)	Temperature (°C.)	Weight (g.)	Refractive Index (25° C.)
1	0.5-0.75	41-54	22.7	1.41386†
2	0.25-0.5	to 79	2.4	1.42197
3	0.5	to 86	0.3	1.42591
4	0.5-0.75	86-89	5.2	1.42985
5	1.0	to 90.5	6.9	1.43056
6	1.0	90.5	12.1	1.43013
7	1.0	90.5-91	7.6	1.43044
8	1.0	91	8.1	1.43118
9	1.0	91-97	0.3	1.44443

†Unreacted malonic ester. Handbook gives $N_D^{20} = 1.4143$.

(0.2 mole) of diethyl malonate and 100 ml. of absolute ethanol. Ethanolic sodium ethoxide (from 9.2 g., 0.4 mole) of sodium in 150 ml. of absolute ethanol) was added over a 20-minute period and the resulting mixture was stirred at room temperature for 24 hours.

An additional 28.8 g. of the amine salt was added followed by another 9.2 g. of sodium "dissolved" in 150 ml. of absolute ethanol. After stirring for an additional 24 hours the alcohol was removed using an aspirator and a hot water bath. The residue was shaken with 50 ml. of ether and sufficient cold water added to dissolve the salt. Following separation of the organic layer, the aqueous layer was extraced five times with equal volumes of ether. The extract was dried and the solvent removed to leave 30 g. of a dark oil. This material, Product C, was

transferred to a still pot using a small quantity of acetone and then fractionated through a 60-plate column yielding the fractions shown in Table 8.

Table 8. Fractionation of Product C

Fraction	Pressure (mm. Hg)	Temperature (°C.)	Weight (g.)	Refractive Index (25° C.)
1	2	to 58	1	1.41591
2	2	58-62	3.7	1.41641
3	1	to 62	2.5	1.42792
4	1	to 91	0.5	1.42977
5	1	91-92 (96 at 2mm.)	2.1	1.43000
6	0.5	80-85 (96 at 2mm.)	2.1	1.43070
7	1	91 (85.5 at 0.75 mm.)	5.8	1.43099
8	1	to 97.5	1.4	1.43752
9	3.5	137-138	2.1	1.44633

Fractions 5, 6, and 7 correspond to the material isolated from the previous preparation of the monosubstituted malonic ester. Fraction 9 was a light yellow oil and was presumed to be the desired product. The yield of disubstituted malonic ester was only 3.5 per cent of the theoretical, based upon amine hydrochloride used. The yield of the monosubstituted compound was 43.3 per cent, based upon the malonic ester used.

The dry-ice trap contained 7.6 g. of material possessing an amine-like odor. This material was fractionated at atmospheric pressure. Three g. of material boiling at 55-57° C (acetone) was collected, the remainder of the material distilling up to 96° C. with no period of constant

temperature. The acetone and the higher boiling material possessed an amine-like odor. It may be possible that a gaseous amine is produced during the reaction or distillation. In fact, during the time the acetone was being collected a basic vapor was apparent (odor and indicator paper) at the neck of the receiver.

In a similar preparation where the reaction mixture was heated to 80° C. for about 72 hours, no material boiling above room temperature at 5 mm. was obtained.

Diethyl Bis(2-dimethylaminoethyl)malonate from Diethyl 2-dimethylaminoethylmalonate.--To a mixture of diethyl 2-dimethylaminoethyl malonate (18 g., 0.078 mole) and dimethylaminoethylchloride hydrochloride (12 g., 0.0833 mole) was added sodium t-butoxide (0.167 mole) in 475 ml. of t-butyl alcohol. The mixture was vigorously stirred and rapidly heated to reflux. The current was shut off and the mixture allowed to come to room temperature without removing the heating mantle. After stirring for two days, heat was again applied until refluxing occurred. Stirring and heating were stopped and the salt allowed to settle. After removing the salt, the alcohol was evaporated at reduced pressure and the residual oil, product D, fractionated at 2 mm. through a five-inch Vigreaux column. The fractions collected are given in Table 9. A portion of the last fraction (number 4), which is believed to be the desired product, yielded a gummy amide derivative when treated with ammonium hydroxide. This amide could not be obtained in crystalline form. Fraction number 4 formed a solid methiodide when treated with excess cold methyl iodide. (Vigorous reaction occurred with considerable evolution of heat.) The product was recrystallized from ethanol as pale yellow needles that melted at 242.5° C.

(unc) with evolution of a basic gas. The melt resolidified and upon further heating darkened at 270° C and melted at 285-300° C. (unc).

Table 9. Fractionation of Product D

Fraction	Pressure (mm. Hg)	Temperature (°C.)	Weight (g.)	Refractive Index (25° C.)
1	1.8	to 98	0.7	1.4325
2	1.8	98-100	0.7	1.4337
3	1.8	to 127	0.4	1.4404
4	1.8	127-128	3.0	1.4450

Calculated for the methiodide, $C_{17}H_{36}N_2O_2I_2$: N = 4.78; I + 43.29 per cent

Found: N = 4.91; I = 43.47 per cent

Attempted Preparation of Diethyl Bis(2-dimethylaminoethyl)malonate from Diethyl 2-Dimethylaminoethylmalonate.--The monoamine ester, 34.4 g. (0.148 mole) and 26.6 g. (0.185 mole) of dimethylaminoethylchloride hydrochloride were stirred in 100 ml. of absolute ethanol and 7.66 g. (0.333 g. at.) of sodium "dissolved" in 200 ml. of absolute ethanol was added over a 35-40 minute period. The resulting mixture was stirred for 20 hours at room temperature. After removing the alcohol by distillation at water aspirator pressure the residue was treated with ether and just enough water to dissolve the salt. The layers were separated and the aqueous layer extracted five times using an equal volume of ether each time. The combined ether solutions were dried over anhydrous sodium sulfate and evaporated to leave only 18.9 g. of oil. Upon distillation this oil, product E, yielded the fractions shown in Table 10. In addition to these fractions, a small quantity of unidentified basic material collected in the dry-ice trap.

Table 10. Fractionation of Product E

Fraction	Pressure (mm. Hg)	Temperature (°C.)	Weight (g.)	Refractive Index (25° C.)
1	0.5	to 80	1.2	1.42920
2	0.5	80-85	5.7	1.43145
3	0.25	78-82	3.1	1.43284
4	0.25	to 108	8-10 drops	1.44449

The main portion of the material isolated by the distillation was the starting material. The last fraction (8-10 drops) may be impure product. Since this material was somewhat soluble in water, the aqueous solution, which had been extracted with ether, was made acidic (hydrochloric acid) and evaporated to dryness. The solid residue was treated with hot ethanol to extract any amino acid hydrochlorides. When the alcohol was cooled, a white hygroscopic solid separated, the solid, washed well with absolute ethanol and dried in a vacuum desiccator, weighed 2.5 g. and melted at 140-145° C. Analysis for halogen (Volhard) indicated that it was γ-dimethylamino butyric acid hydrochloride, which would have come from the starting material.

Calculated for $C_6H_{14}NO_2Cl$: Cl = 21.16 per cent

Found: Cl = 20.81 per cent

Further proof that little or no reaction had taken place was obtained by examination of a white solid which slowly separated from the alcohol that had been distilled from the reaction mixture. This solid, which was powdery, was obtained as clusters of white needles from moist ethanol. It did not melt below 360° C. but was organic, as shown by the

fact that it charred when warmed with sulfuric acid, and burned completely when held in a burner flame. Analysis for halogen (Volhard) indicated an empirical formula corresponding to the free base of the starting material.

Calculated for $C_4H_{10}NCl$: Cl = 32.97 per cent

Found: Cl = 32.70 per cent

The compound is undoubtedly N,N,N',N'-tetramethylpiperizinium dichloride and resulted from dimerization of the unreacted free base.[30]

Attempted Preparation of 5,5-Bis(dimethylaminoethyl)barbituric Acid from Diethyl Bis(2-dimethylaminoethyl)malonate.--To 60 ml. of isopropyl alcohold in which had been "dissolved" 0.6 g. (0.026 g. at.) of sodium, was added 0.72 g. of urea (0.012 mole). This mixture was stirred and 1.2 g. of diethyl bis(2-dimethylaminoethyl)malonate added (i.e., fraction 4, see Table 9). After refluxing for 36 hours, the mixture was cooled to 5° C. and excess gaseous hydrogen chloride introduced. Removal of the solvent yielded an oily residue which was taken up in a small amount of water. Saturated ammonium chloride solution (20 ml.) was added and the pH adjusted to 7.2 using hydrochloric acid and ammonium hydroxide. The resulting solution was extracted 10 times with 20-ml. portions of chloroform. The chloroform solution dried and evaporated by warming at reduced pressure. A gummy residue remained which resisted attempts to bring about crystallization.

Syntheses of Spiro-amino Barbituric Acids Via 5,5-Bis(2-iodoethyl)barbituric Acid

Introduction.--The reactions described herein and outlined in Figure 15 represent an attempt to prepare the desired spiro-amino barbituric acids without using the vesicant nitrogen mustards.

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[30] F. K. Beilstein, Handbuch Der Organischen Chemie, Vierte Auglage. Berlin: Julius Springer, 1922, Vierter Band, p. 113.

It was believed that the ether linkage of diethyl tetrahydropyran-4,4-dicarboxylate, I, and/or the spiro-barbituric acid, II, derived from it could be cleaved to give the corresponding dihalo compounds. The dihalide from the ester, III, should be capable of reacting with primary amines to give amino esters, V, that could be converted into the desired spiro-amino barbiturates, VI. Alternately the dihalo barbituric acid, IV, when reacted with primary amines should give the desired products directly.

Attempts to cleave the ester-ether were entirely unsatisfactory; more promising was cleavage of the barbituric acid, derived from the ester, to the desired bis(2-haloethyl)barbituric acid.

Attempts to react the dihalo barbiturate with primary amines have been successful. Spiro-1'-methylpiperidine-4',5-barbituric acid prepared by this procedure gave correct analysis for carbon, hydrogen and nitrogen. Various other spiro-amino barbituric acids have been prepared by this procedure and have given the correct analysis for nitrogen content.

Preparation of Diethyl Tetrahydropyran-4,4-dicarboxylate.--This ester was prepared using the method suggested by Harnest and Burger.[31]

Six-hundred-eight ml. (641 g.: 4 moles) of redistilled diethyl malonate was added to a solution of 92 g. (4 g. at.) of sodium dissolved in a liter of absolute ethanol contained in a three-necked, round-bottomed flask of five-liter capacity, fitted with a stainless steel stirrer, a dropping funnel, and a reflux condenser. After the mixture has refluxed for about five minutes, 468 ml. (572 g.; 4 moles) of redistilled commercial β,β'-dichlorodiethyl ether was added, and the mixture refluxed with

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[31]G. H. Harnest, and A. Burger, J. Am. Chem. Soc., 65, 370 (1943).

stirring overnight. It was then cooled and another 92 g. of sodium dissolved in a liter of absolute ethanol added. Following refluxing for 48 hours, heating and stirring were stopped. The sodium chloride was allowed to settle out, and the liquid portion decanted and filtered. The alcohol was distilled from the reaction mixture, the residue treated with 300 ml. of water, and extracted three times with 200-ml. portions of ether. The extracts were combined and dried over anhydrous sodium sulfate. Following evaporation of the ether, the diethyl tetrahydropyran-4,4-dicarboxylate was distilled. The yield of the fraction distilling at 125-135° C. (9-10 mm.) was 470 g. (51 per cent).

Another preparation yielded only 385 g. (boiling point 103° C. at 2 mm.) and contained a considerable amount of higher boiling material which was fractionated through a 12-inch "heli pac" column to give:

23.3 g. distilling at 142-144° C/4 mm. pressure

24.0 g. distilling at 150-200° C/2-5 mm. (mainly at 200° C./5 mm. pressure

17.5 g. distilling at 217-220° C/7-13 mm. pressure.

Difficulty was encountered in maintaining the pressure due to some decomposition of the material in the pot. These materials were not identified. They possibly are di-diethyl malonic ester derivatives, Figure 18a or carbitol-type malonic esters. Figure 18b.

Attempted Preparation of Diethyl Bis(2-bromoethyl)malonate.--To 190 g. of 40 per cent hydrobromic acid (equivalent to 75 g. of hydrogen bromide or 0.93 mole) in a 250-ml. round-bottomed flask, equipped with an efficient water condenser, were added 45 g. of concentrated sulfuric acid and 35.4 g. (0.154 moles) of diethyl tetrahydropyran-4,4-dicarboxylate. The resulting red-brown homogeneous mixture was then refluxed for 12 hours.

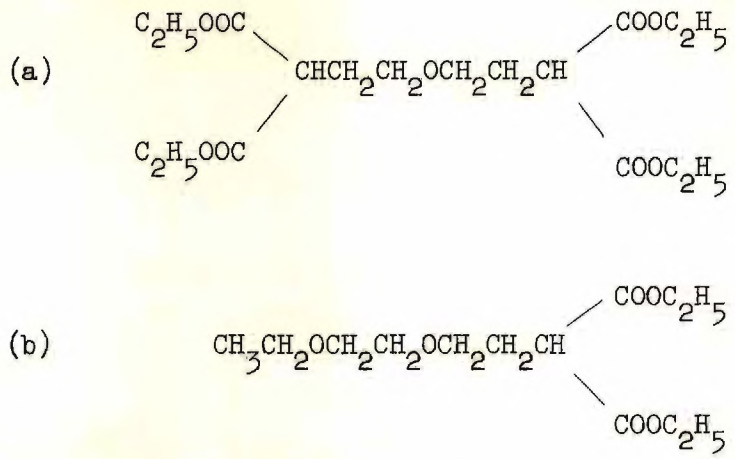

Figure 18. Proposed By-products from Preparation of Diethyl Tetrahydropyran-4,4-dicarboxylate.

Ethyl bromide was evolved during the reaction, indicating that hydrolysis of the ester occurred. Upon cooling the reaction mixture, a considerable quantity of pale yellow crystalline material separated. The whole of the mixture was continuously extracted with ether for two days with no attempt to isolate the crystalline material. The ether extract was then dried with anhydrous sodium sulfate and the ether was removed by means of a water aspirator.

The resulting syrupy liquid, which contained some yellow crystalline material, was dissolved in excess absolute ethanol (approximately 600 ml.) and acidified with a small amount of hydrobromic acid. After standing at room temperature for two days, 300 ml. of dry toluene was added and the mixture distilled slowly until the temperature of the distillate reached 78° C. (Toluene, ethanol, and water distill as an azeotrope slightly below this temperature.) The distillate was dried overnight with anhydrous calcium sulfate and returned to the distilling flask and the mixture was again distilled slowly until the temperature of the distillate

reached 78° C. Most of the remaining toluene and alcohol were removed by distilling under reduced pressure until the volume remaining was about 50 ml.

This material was treated with cold, concentrated potassium carbonate solution to separate any acidic material, and then extracted several times with ether. After drying over anhydrous calcium sulfate, the ether was removed by reduced pressure distillation, and the remaining yellowish liquid distilled through a short column. A small amount of material (10-15 drops) distilled below 108° C. (mainly at 92° C.) under a pressure of 2-3 mm. The remaining liquid, except for a small amount of material that was held by the still, boiled at 108-109° C. at 2-3 mm. and weighed 9.5 g. This neutral compound gave a negative test for halogen and appeared to be the starting material.

An amide derivative was prepared by mixing approximately 1.5 g. of this material with 20 ml. of concentrated ammonium hydroxide in a 25 ml. Erlenmeyer flask and allowing the mixture to remain for four days at about 30° C., with occasional shaking. The excess ammonium hydroxide and water were removed by reduced pressure distillation and the clear viscous liquid was dissolved in hot absolute ethanol and filtered. The amide crystallized from the solution when cooled. After filtering and washing with a small amount of ether, the amide melted at 156.5-157° C. (unc). A mixed melting point determination with an authentic sample of the amide of diethyl tetrahydropyran-4,4-dicarboxylate (prepared in the same manner) showed no depression.

Ethyl Tetrahydropyran-4-carboxylic Acid-4-carboxylate.--The potassium carbonate solution that was used to extract the acidic materials in the

previous experiment was cooled in an ice-water bath and acidified with cold sulfuric acid. After warming to expel traces of ether, this acid solution was cooled. An oil separated but, after a few minutes of stirring, crystallized to white needles. These were readily soluble in ether, fairly soluble in water, and melted over a range of 7-8° C. They were purified by dissolving in dilute sodium hydroxide, extracting the solution with ether, warming to expel the remaining traces of ether, and reacidifying with sulfuric acid. One recrystallization was effected from water. The crystals that separated were dried for several days in a desiccator and the following constants determined:

Melting point	97.5-98° C. (unc)	
Neutralization equivalent 203.	Calculated for $C_9H_{14}O_5$	NE 202
Saponification equivalent 99.	Calculated for $C_9H_{14}O_5$	SE 101

The acid formed in the saponification reaction was isolated by evaporating the basic solution to a volume of about 25 ml., washing the solution well with ether, acidifying with sulfuric acid and then extracting with six 25-ml. portions of ether. Evaporation of the ether yielded a small amount of light tan colored solid which, after recrystallization from ether-petroleum ether, melted at 171-172° C. (unc). At a slightly higher temperature, carbon dioxide was evolved. The resulting clear liquid solidified upon cooling and when reheated melted at 86-87° C. (unc). Tetrahydropyran-4,4-dicarboxylic acid melts at 172-173° C. and tetrahydropyran-4-carboxylic acid melts at 87° C.[32]

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[32] G. H. Harnest and A. Burger, J. Am. Chem. Soc., 65, 370 (1943); G. S. Gibson, and J. D. A. Johnson, J. Chem. Soc., 1930, 2525; J. von Braun, and Z. Kohler, Ber. deut. Chem. Ges., 50, 1685 (1917).

As an added confirmation that the compound was the heretofore unreported monoester, it was prepared by another method. Since diethyl tetrahydropyran-4,4-dicarboxylate could be used instead of diethyl phthalate in Smith's method[33] for preparing absolute ethanol, and since the desired compound would result from this reaction, the following procedure was used. Approximately 1.8 liters of absolute ethanol was placed in a two-liter flask fitted with a stirrer and a condenser equipped with a drying tube. Clean sodium (14 g.) was introduced into the alcohol and when it all had been added, 60 g. of diethyl tetrahydropyran-4,4-dicarboxylate was introduced. The resulting solution was heated at 50-60° C. overnight and the dried alcohol was distilled until there remained about 200 ml. of material in the flask. The cooled mixture was filtered after adding 50 ml. of ether and the collected solid washed well with ether and then dissolved in a minimum quantity of water. The solution was acidified with sulfuric acid and warmed under reduced pressure to remove traces of ether and ethanol. After cooling the solution in the refrigerator overnight the white needles that separated were collected and recrystallized from water. The yield of the acid-ester (melting at 97-98° C.) was six g. (unc). A mixed melting point determination with the compound isolated from the attempted ether cleavage showed the two substances to be identical.

Attempted Preparations of Diethyl Bis(2-iodoethyl)malonate Using Aqueous Hydriodic Acid.--Hydrogen iodide, prepared from water and phosphorous triiodide, was collected in 36 g. of water. The collection flask was

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[33] E. L. Smith, J. Chem. Soc., 1927, 1289.

kept cold by means of an ice bath and the preparation was discontinued when the increase in weight amounted to 65.5 g. The resulting solution, containing 0.512 mole of hydrogen iodide, was mixed with 14.75 g. (0.064 mole) of diethyl tetrahydropyran-4,4-dicarboxylate in a 200-ml. round-bottomed flask equipped with an efficient condenser. The mixture was warmed slowly until fumes of hydrogen iodide were detected at the top of the condenser. The heat was then removed and the reaction mixture allowed to stand overnight. It was slowly brought to reflux and heated for seven hours. After cooling, there appeared to be some solid material and some oily material in the bottom of the reaction flask. These two portions (oil and solid) were drawn off together and the acid layer extracted three times with 50 ml. of ether. The ether extracts were combined with the previously separated solid and liquid and washed first with saturated sodium bicarbonate and then with water. (Upon acidifying these washes, no organic material separated.) The ether solution was dried over anhydrous sodium carbonate, and after removal of the ether yielded a small amount of dark liquid. This was washed with cold sodium bisulfite solution and again extracted with ether. The ether was evaporated after washing once with water and drying, leaving just a few small crystals. These almost white, hexagonal crystals melted at about 107-109° C. (unc) after recrystallizing once from water. The crystals appeared to be only slightly soluble in water yet were slow about recrystallizing. Since there was such an insignificant amount, no further investigation was feasible. Evidently, the major portion of the ester was hydrolyzed to the diacid which is soluble in water.

Attempted Preparation of Diethyl Bis(2-iodoethyl)malonate Using Hydriodic Acid in Water-Acetic Anhydride.--Aqueous hydriodic acid (130 g. of 55-58 per cent) was introduced into a three-liter, three-necked flask fitted with a dropping funnel and an efficient condenser. By means of the dropping funnel, 14.75 g. (0.064 mole) of diethyl tetrahydropyran-4,4-dicarboxylate in 230 g. of acetic anhydride containing traces of hydriodic acid was introduced at such rate that the heat generated was insufficient to cause violent boiling (too rapid addition at one time caused the loss of some of the reaction mixture through the condenser). After the addition of all the ester-anhydride solution the reaction flask was heated cautiously at a very gentle reflux for one hour. The dark colored contents of the flask were poured onto about 200 g. of ice. Sufficient potassium carbonate was added to make the aqueous portion basic to litmus. It was then extracted with ether. The extract was dried for several days over anhydrous sodium sulfate, filtered from the drying agent, and evaporated at reduced pressure. The remaining nine g. of reddish liquid was distilled (at 8 mm.) to yield about two g. of dark colored material boiling below 120° C. and 4.1 g. of light reddish liquid that boiled at 126-128° C. The dark colored material was discarded. The reddish liquid was insoluble in water, soluble in ethanol, and gave a positive test for iodine. No further examination was made of this small quantity of material as subsequent cleavage of the barbituric acid derived from diethyl tetrahydropyran-4,4-dicarboxylate was much more promising.

Preparation of 1-chloro-2-iodoethane.--This compound was prepared according to the method of Simpson as described by Thorpe.[34] A cooled suspension

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[34]T. E. Thorpe, J. Chem. Soc., 37, 189, (1880).

of 127 g. (0.5 mole) of finely powdered iodine in 255 ml. of water was treated with a stream of chlorine, shaking until almost all the iodine had disappeared. The resulting yellowish-brown solution was decanted and cooled. Ethylene, generated from the reaction of concentrated sulfuric acid and ethanol, was passed through a solution of sodium bicarbonate and thence into the iodine monochloride solution. After about seven hours the operation was discontinued even though the reaction was not complete (as indicated by the fact that the solution still was light red in color). The dark oily layer was separated, washed with water, with sodium bisulfite solution until colorless, and again with water. The resulting oil was dried over anhydrous calcium chloride, separated from the drying agent and distilled (first at reduced pressure and then at atmospheric pressure). The first distillation resulted in loss of a considerable quantity of material due to its low boiling point at lowered pressure. The fraction that boiled 138-140° C. weighed 41 g. and was slightly pink. This represents a 21.6 per cent yield, based on the iodine used.

Attempted Preparation of Diethyl Bis(2-chloroethyl)malonate.--An ethanolic solution of sodiomalonic ester was prepared by dissolving 2.4 g. (0.105 mole) of sodium in about 800 ml. of absolute ethanol contained in a two-liter, three-necked flask, fitted with a reflux condenser and stainless steel stirring rod and adding 17.85 g. (0.105 mole) of diethyl malonate. This solution was cooled to 0° C., and 20 g. (0.105 mole) of 1-chloro-2-iodoethane was added. This mixture was stirred overnight, allowing the temperature to rise slowly to room temperature. Another 2.4 g. of sodium was "dissolved" in 800 ml. of absolute ethanol and added to the reaction mixture which had previously been cooled to about 10° C.

An additional 20 g. of 1-chloro-2-iodoethane was added and the mixture allowed to approach room temperature spontaneously for about one hour, after which it was heated at a gentle reflux for about 40 hours.

Most of the alcohol was removed by distilling until the volume remaining was about 80 ml. The remaining dark liquid was shaken with 100 ml. of ether and enough water added to give a clear separation of layers. After separation of the ether layer the aqueous layer was extracted with two more 100-ml. portions of ether. The ether solutions were combined, dried over anhydrous calcium sulfate, and the ether removed at reduced pressure. Since the amount of material that remained was rather small, the aqueous portion was extracted again using four 150-ml. portions of chloroform. These extracts were combined with the material from the ether extract and the chloroform was removed by distillation. The residue was fractionated at a pressure of four mm. No constant boiling point was noticed until the distillate temperature reached 65° C. Below this temperature only a very small amount of material, which smelled strongly of chloroform, distilled. The material boiling at 65-69° C. (4 mm.) weighed approximately 10 g. Above this temperature only a few drops of material could be collected. The major portion of this last fraction distilled at 106° C. and gave a faint test for halogen. No further investigation of it was attempted because of the small quantity obtained.

A portion of the major fraction (65-69° C./4 mm.) was converted to the amide derivative as follows. Roughly four ml. of the material and 15 ml. of concentrated ammonium hydroxide were shaken together in a small Erlenmeyer flask. After standing four hours at room temperature, with

frequent shaking, the contents of the flask became homogeneous. The mixture was allowed to stand at room temperature for two days, after which the ammonia and water were removed by reduced pressure distillation. The remaining viscous light yellow liquid crystallized upon cooling and was washed from the flask with hot absolute ethanol. The material was crystallized by adding sufficient water to the boiling ethanol suspension to effect solution, filtering, and cooling. After several recrystallizations, the dry white crystals melted at 165-172° C. (unc). A sample of the amide derivative of malonic ester, prepared in a similar manner, melted at 165-170° C. (unc). A mixed melting point of these two preparations showed no depression. This indicated that the desired reaction did not occur, at least not to any large extent.

Preparation of Spirotetrahydropyran-4',5-barbituric Acid.--Forty-six grams (2 g. at.) of sodium was cut into small pieces and added to two liters of isopropyl alcohol contained in a five-liter flask. The contents were warmed with stirring until all the sodium had reacted. Urea (126 g., 2.1 moles) was added followed by 460 g. (2 moles) of diethyl tetrahydropyran-4,4-dicarboxylate. The mixture was refluxed gently and stirred vigorously for ten hours. (During the reaction period, the mixture became quite pasty and required a sturdy, efficient stirrer.) The mixture was allowed to cool to room temperature and then cooled to 5° C. in a large refrigerator bath. Dry hydrogen chloride was passed into the mixture at such a rate that the temperature was maintained below 10° C. When the contents became fluid and a drop of the mixture gave an acid reaction to indicator paper, the gas flow was stopped. After stirring for about ten minutes longer, the solids were separated by centrifugation.

The alcohol-moist solids were transferred to an empty vacuum desiccator and aspirator pressure was applied for 20 minutes to remove some of the excess hydrogen chloride. The solid was shaken well with about two liters of cold (5° C.) water, and the insoluble crude barbituric acid derivative collected by filtering. The yield of dried material was 200 g., 43.5 per cent. After recrystallizing from 2.5 liters of water containing 500 ml. of isopropyl alcohol, there was 180 g. (36 per cent) of product melting at 218-220° C. (unc).

The centrifugate obtained from the original reaction mixture was evaporated under reduced pressure and the residue shaken with 500 ml. of cold water. Drying the oily organic layer over silica gel, followed by fractionation yielded 90 g. of unreacted ester distilling at 85-86° C. at 0.5 mm. pressure. Based upon the actual amount of ester consumed (370 g.) during the reaction, the yield of purified product (monohydrate)[35] was 52.5 per cent of the theoretical amount. Some other preparations of this same material are described below since seemingly slight variations in the procedure had a marked effect upon the yield of product.

Forty-six g. of clean sodium (2 g. at.) was added in small pieces, as rapidly as reaction would allow, to two liters of isopropyl alcohol. When all the sodium had reacted, 120 g. (2 moles) of urea was added with stirring. Diethyl tetrahydropyran-4,4-dicarboxylate (230 g., 1 mole) was then added and the resulting mixture refluxed, with stirring, for 24 hours. The reaction mixture was cooled and the salts were separated from the alcohol using a laboratory basket centrifuge. The mass of salts, still

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[35] O. Kamm and J. H. Waldo, J. Am. Chem. Soc., 43, 2223 (1921).

moist with alcohol, was divided into two approximately equal portions. One portion was suspended in 250 ml. of isopropyl alcohol and treated with 46 g. of hydrogen chloride gas in 150 ml. of isopropyl alcohol. This mixture was shaken well and allowed to stand for several days in the refrigerator. The solids were separated (basket centrifuge) and dried free of alcohol using aspirator pressure and a warm water bath. Dissolving the solids in a minimum amount of water and cooling the solution effected crystallization of 12 g. of the product as the monohydrate. (An air-dried sample when dried at 110° C. for 12 hours decreased in weight 8.44 per cent; calculated weight loss for the monohydrate would be 8.33 per cent.) The material melted at 218-220° C. (unc).

The second portion of alcohol-moist salt was added to a mixture of concentrated hydrochloric acid (in excess) and ice, keeping the temperature below 0° C. After shaking well, the solid that remained was separated by filtering and recrystallizing from water. There resulted 12.6 g. of the product melting at 218-220° C. (unc).

The overall yield from both portions was only 14.6 per cent of the theoretical.

Another preparation using the second method of acidification resulted in a 12.8 per cent yield. From this preparation a considerable amount of crude tetrahydropyran-4,4-dicarboxyclic acid was isolated (37 per cent based upon the weight of ester used). In all probability the yield of desired product was low because of hydrolysis. Another slightly smaller run (1.75 moles of the diester) was worked up by the second method using only a 0.5 mole excess of hydrochloric acid and maintaining the temperature at 0° C. or below. This resulted in a yield

of 34.7 per cent of the crude spiro-barbituric acid melting at 217-220° C. (unc).

Attempts to prepare this compound by dissolving the salts in cold water and then acidifying with hydrochloric acid at 0° C. were not successful. The acidic compound which was isolated apparently was a crude tetrahydropyran-4-carboxy-4-carbonylureide (25 per cent of the theoretical). It melted at 234.5-235° C. (unc) after recrystallization from water and had a neutralization equivalent of 330 ± 2. An additional recrystallization from isopropyl alcohol yielded a solid melting at 236-236.5° C. (unc) with a neutralization equivalent of 320 ± 2. This solid lost carbon dioxide when heated at 88° C. under a vacuum of about 29 inches of water. The sample lost 13.85 per cent of the original weight. This value is 66.7 per cent of the theoretical. The neutralization equivalent was high by an amount indicating a purity of 67.4 per cent. The remainder is presumably the decarboxylated compound. Repeated recrystallizations resulted in a non-acidic white solid melting at 239.5-240° C. (unc). This compound was tetrahydropyran-4-carbonylureide.

Calculated for $C_7H_{12}N_2O_3$: C = 48.83; H = 7.03; N = 16.27

Found: C = 48.97; H = 6.97; N = 16.29

A small (unweighed) sample of this compound was hydrolyzed by refluxing in 0.5 molar sodium hydroxide. The resulting acid was isolated by evaporating the hydrolysis mixture to dryness, adding ether to the salts, and passing dry hydrogen chloride into the salt suspension. Sufficient water was added to dissolve the sodium chloride produced. The ether layer was separated, dried, and evaporated to leave a solid, white acid that melted without further purification at 87-88° C. (unc). This

corresponds to the melting point of tetrahydropyran-4-carboxylic acid. A mixed melting point showed no depression.

Stability of Spirotetrahydropyran-4',5-barbituric Acid in Basic Medium.--It has been reported that 5,5-disubstituted barbituric acids are precipitated from a solution of their sodium salts by the addition of carbon dioxide.[36] It was found that spirotetrahydropyran-4',5-barbituric acid did not crystallize when a solution of the sodium salt (from sodium hydroxide and the acid) was so treated. This suggested a rather rapid hydrolysis. Therefore, a solution of 1 g. of the barbituric acid monohydrate in sodium hydroxide (0.5 g. in 10 ml. of water) was allowed to stand at room temperature for 15 minutes and then acidified with hydrochloric acid. The white solid that separated melted at 217-220° C. (unc) with evolution of a gas. Presumably, this solid was the crude tetrahydropyran-4-carboxy-4-carbonylureide. When this solid was redissolved in sodium hydroxide solution, allowed to stand at room temperature for 24 hours and then acidified, the solid that separated was tetrahydropyran-4,4-dicarboxylic acid. It melted at 172-174° C. (unc) with evolution of carbon dioxide. The melt, after solidifying, remelted at 85°-87° C. (unc). This ease of basic hydrolysis accounts for the fact that the spiro-barbituric acid cannot be prepared from an aqueous solution of the crude sodium salts. A similar situation has been reported with a five-membered spiro-barbituric acid,[37] and more recently for

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[36] E. M. van Heyningen, J. Am. Chem. Soc., 76, 2241 (1954).

[37] G. S. Skinner, G. Limperos, and R. H. Pettibone, J. Am. Chem. Soc., 72, 1648 (1950).

spiro-1'-benzenesulfonylpiperidine-4',5-barbituric acid.[38] This latter compound represents the first reported example of a spiro-barbituric acid incorporating a piperidine ring.

Stability of Spirotetrahydropyran-4',5-barbituric Acid in Acidic Medium.--One gram of the monohydrate of spirotetrahydropyran-4',5-barbituric acid was heated for 75 minutes on a steam bath with 5 ml. of concentrate sulfuric acid. During the heating the solution became light brown in color. This solution was poured into a mixture of ice and water (20 g.) and the white needles that separated were filtered, washed with water, and recrystallized once from water. There resulted 0.7 g. (70 per cent recovery) of the original compound melting at 218-219° C. (unc).

In addition to the above test, a small sample of the material was recrystallized from 25 ml. of distilled water to which had been added six drops of concentrated hydrochloric acid. The compound was washed well with water and dried. It was shown to be the original compound by a mixed melting point.

Attempted Preparations of 5,5-Bis(2-bromoethyl)barbituric Acid.--One gram of spirotetrahydropyran-4',5-barbituric acid (monohydrate) was treated with five ml. of 30 per cent hydrobromic acid in acetic acid. This mixture was warmed until there was a pronounced evolution of hydrogen bromide and then allowed to stand at room temperature for 40 hours. After heating to 80° C., the yellow solution was poured onto 20 g. of crushed ice.

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[38] G. S. Skinner, H. R. Krysiak, and J. A. Perrigrino, J. Am. Chem. Soc., 77, 2248 (1955).

There resulted an essentially quantitative recovery of the starting material, melting at 217-219° C. (unc). The identity was proven by a mixed melting point with a known sample.

In a second attempt, 5.04 g. (0.025 mole) of spirotetrahydropyran-4',5-barbituric acid (monohydrate) was added to 25.3 g. (0.15 mole) of 48 per cent hydrobromic acid containing 7.4 g. of concentrated sulfuric acid. This mixture was heated slowly to 110° C. and held at this temperature for 8 hours. During this heating a considerable quantity of hydrogen bromide was evolved. When cooled, the resulting red mixture contained only a trace of insoluble oil. It was, therefore, refluxed for an additional 12 hours. Upon cooling, the mixture (now coffee colored) deposited some crystalline material as well as the insoluble oil. The mixture was treated with 25 ml. of cold water whereupon the solid dissolved. An additional 50 ml. of cold water was added and the mixture was extracted five times with 50-ml. portions of ether. The ether extracts were washed once with 25 ml. of cold water, dried over $CaCl_2$, and the ether evaporated. There resulted 3.5 g. of a red-yellow liquid. This material could not be made to crystallize and was not examined further.

In a third cleavage attempt, essentially anhydrous hydrogen bromide generated from potassium bromide and 96 per cent phosphoric acid, was used.

A mixture of 123.6 g. of 96 per cent phosphoric acid (from 100 g. of 86 per cent phosphoric acid and 23.6 g. of phosphorus pentoxide), 40 g. (0.4 mole) of sodium bromide, and 21.6 g. of spirotetrahydropyran-4',5-barbituric acid (monohydrate) was shaken vigorously for 10 hours while maintaining the temperature at 150° C. The reaction mixture was

contained in a 500-ml. round-bottomed flask with ST joints. An air condenser was inserted in one opening to allow gases to escape and a thermometer was inserted in a second opening. The third opening was closed with a glass stopper. The flask was heated by means of an electrically powered mantle; the portion of the flask exposed above the mantle was covered with glass wool. The entire assembly was then clamped firmly in a laboratory shaker. After shaking, the mixture which was quite dark was poured onto 400 g. of crushed ice and water. No solid material separated and the small quantity of black tar that formed was not examined.

5,5-Bis(2-iodoethyl)barbituric Acid.--This preparation was based upon the procedure of Stone and Schechter.[39]

A mixture of 200 g. of 96 per cent phosphoric acid (prepared from 86 per cent phosphoric acid and phosphorous pentoxide using a weight ratio of 1/0.236), 100 g. of potassium iodide (0.6 mole), and 43.2 g. (0.2 mole) of spirotetrahydropyran-4',5-barbituric acid (monohydrate) was shaken vigorously for 10 hours while maintaining the temperature at 135° C. The resulting dark solution was poured, while warm, onto 400 g. of crushed ice. A yellow solid that separated was removed by filtering and was washed well with cold water. The yield of crude 5,5-bis(2-iodoethyl)barbituric acid [melting at 205-208° C. (unc)] was 65 g. or 74.6 per cent of the theoretical amount. Any unreacted starting material contained in the crude diiodide was conveniently removed by washing well with hot water (60° C.). Recrystallization from dioxane-water mixtures gave the pure product that melted with decomposition at 207-208° C. (K)

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[39]H. Stone and H. Schechter, J. Org. Chem., 15, 491 (1950).

when placed in the melting point apparatus at 203° C. and heated rather rapidly. The product was analyzed as follows:

Calculated for $C_8H_{10}N_2O_3I_2$: C = 22.04; H = 2.27; N = 6.44; I = 58.2 per cent

Found: C = 22.05; H = 2.31; N = 6.42; I = 58.0 per cent

Other runs using slightly different concentrations of phosphoric acid yielded considerably less product. These runs yielded from 16.0 to 68.8 per cent of the theoretical amount.

Other Attempted Preparations of 5,5-Bis(2-iodoethyl)barbituric Acid.--Upon standing at room temperature for 40 hours in an aqueous solution of hydriodic acid (specific gravity of 1.5), spirotetrahydropyran-4',5-barbituric acid (monohydrate) was unchanged. The identity of the material isolated (80 per cent recovery) was established by means of a mixed melting point determination.

One gram of spirotetrahydropyran-4',5-barbituric acid (monohydrate) when heated at 80° C. for 45 minutes with aqueous hydriodic acid (specific gravity of 1.5) reacted to some extent. A white solid (0.65 g.) was isolated by cooling the reaction mixture to 0° C., filtering, and washing the solid with cold water. This product melted at 179-185° C. (unc). However, the material gave only a weak test for iodine and after repeated recrystallizations from ethanol yielded a solid that proved to be the starting material.

Spiro-1'-methylpiperidine-4',5-barbituric Acid.--5,5-Bis(2-iodoethyl) barbituric acid (analytical sample) (4.735 g., 0.01086 mole) was suspended in 100 ml. of absolute ethanol, and 3.40 ml. (0.01086 mole) of an ethanolic solution of methyl amine containing 10 g. of amine per 100 ml. was

added. The resulting mixture, contained in a 250 ml. glass-stoppered bottle, was shaken mechanically for one hour in the dark at room temperature.

During this period of shaking, 0.0217 mole of silver oxide was prepared by adding 20 per cent sodium hydroxide in slight excess to 3.69 g. of silver nitrate dissolved in water. The solid was washed free of sodium hydroxide with cold water and then most of the water removed by washing three times with absolute ethanol.

One-half of the silver oxide was added to the reaction mixture and shaking continued for 30 minutes. After this period of time no silver oxide remained (indicated by the absence of the brown color). The remainder of the silver oxide was added and the shaking continued for an additional hour. The reaction mixture was allowed to stand at room temperature for eight hours, warmed to 65° C., and filtered. The solid was washed several times with hot ethanol, and the washes collected with the original filtrate. After cooling the filtrate and adding excess ether, 2.1 g. (91.5 per cent) of a white solid was obtained [melting at 155-159° C. (unc) with evolution of a basic gas]. The melting point varied slightly with the rate of heating and with the temperature at which the sample was placed into the apparatus. The solid was found to be insoluble in ether or ethyl acetate but soluble in water to the extent of 120 g. per 100 g. of water. It was also soluble in hot ethanol, hot isopropyl alcohol, and hot n-butyl alcohol but did not crystallize readily when these solutions were cooled. It was only slightly soluble in acetone (absolute). The amino-barbiturate was crystallized once from absolute acetone (required about 500 ml. of solvent per g.) as white needles (1.4

g.: 66.6 per cent recovery). The yield of product melting at 159-160° C. (unc) was 61.0 per cent. After repeated recrystallizations from ethanol-acetone mixtures, the product melted with decomposition at 160-160.5° C. (unc) or at 164-166° C. (K).

Calculated for $C_9H_{13}N_3O_3$: C = 51.18; H = 6.20; N = 19.89 per cent

Found: C = 51.45; H = 6.19; N = 20.07 per cent

A one-tenth molar preparation of spiro-1'-methylpiperidine-4',5-barbituric acid using essentially the same procedure and a less highly purified 5,5-bis(2-iodoethyl)barbituric acid resulted in a crude yield of 14.3 g. (67.8 per cent).

Prior to this successful preparation, an attempt had been made to effect the N-methylpiperidine ring formation by more drastic reaction conditions, i.e., sealed tube reaction with excess methylamine at 100° C. for 8 hours. No solid material was obtained from this reaction and the iodine-containing oil that resulted was not identified.

In addition, another run was made using two equivalents of methylamine and heating the mixture in a sealed glass container at 85-90° C. for 17 hours with ethanol. Freshly prepared silver oxide (in the calculated amount) was added at room temperature and mixed well by shaking mechanically. The resulting silver iodide was removed by filtering. Evaporation of the solvent left a small amount of yellow oil that was caused to crystallize by taking up in a minimum quantity of ethanol and cooling to -10° C. There resulted a minute quantity of hygroscopic white needles melting at 225-230° C. (unc). This material was not examined further.

Spiro-1'-ethylpiperidine-4',5-barbituric Acid.--A mixture of 2.25 g. (0.05 mole) of ethylamine and 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)barbituric acid was suspended in 350 ml. of absolute ethanol in a 500-ml. glass-stoppered bottle and mechanically shaken at room temperature. The materials reacted quite rapidly as indicated by the fact that almost immediately after mixing, a small portion gave a positive test for iodine ion. Silver oxide was prepared from an aqueous solution of 8.5 g. (0.05 mole) of silver nitrate by adding a slight excess of 20 per cent sodium hydroxide. The silver oxide was washed free of sodium hydroxide with water and then washed several times with small portions of absolute ethanol. This silver oxide was added to the reaction bottle after 1.75 hours. Shaking was continued for 10 hours although the silver oxide was rapidly converted to silver iodide. A second equal portion of freshly prepared silver oxide was then added and the shaking was continued for an additional 10 hours.

The mixture was filtered to remove the silver iodide and the silver iodide washed with 50 ml. of absolute ethanol. Evaporation of the alcohol left 6.5 g. of crude product. Extraction of the silver iodide with hot alcohol yielded an additional 4 g. This crude material (10.5 g.) represents a 93 per cent yield. One recrystallization from absolute ethanol yielded a 90.5 per cent recovery of water soluble white crystals that melted at 161-163° C. (unc). An analytical sample was prepared by recrystallization from ethanol. This material melted with decomposition at 166-167° C. (K) when placed in the apparatus previously heated to 155° C.

Calculated for $C_{10}H_{15}N_3O_3$: N = 18.66 per cent

Found: N = 18.84 per cent

Spiro-1'-(2-hydroxyethyl)piperidine-4',5-barbituric Acid.--To a methanolic suspension (350 ml.) of 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)-barbituric acid was added 3.05 g. (0.05 mole) of ethanolamine. The resulting mixture was shaken for three hours at room temperature. Freshly prepared (0.05 mole) silver oxide was added and shaking was continued for nine hours although the dark color of the silver oxide was discharged almost at once. Another similar addition of silver oxide was made and shaking was continued for 12 hours. As before, the oxide was rapidly converted to silver iodide.

The silver iodide was removed by filtering. After removing the alcohol from the filtrate at reduced pressure, a gummy mass resulted. This was dissolved in methanol (50 ml.) and treated with sufficient acetone to cause separation of some amorphous solid. The solid was removed by filtration and the filtrate was evaporated to dryness. The residue was taken up in a minimum amount of methanol and treated to the cloud point with acetone. Upon cooling, a crystalline material was obtained. Recrystallization was effected from methanol to yield 3.5 g. (29 per cent of the theoretical) of a water soluble product melting with decomposition at 267-268° C. (unc). When placed in the Kofler hot-stage micro-melting point apparatus at 260° C. this solid changed form from plate-like crystals to needles at about 265-270° C. and melted with decomposition at 277-278° C. (K). A tendency to sublime was noted at the point of crystalline transformation.

Calculated for $C_{10}H_{15}N_3O_4$: N = 17.42 per cent

Found: N = 17.46 per cent

Spiro-1'-allylpiperidine-4',5-barbituric Acid.--To a suspension of 8.75 g. (0.02 mole) of 5,5-bis(2-iodoethyl)barbituric acid in 100 ml. of reagent grade methanol was added 1.14 g. (0.02 mole) of allylamine. The amine was added as 10 ml. of a methanolic solution containing 11.4 g. per 100 ml. The mixture was shaken mechanically for 1.25 hours at room temperature in a glass-stoppered bottle. Silver oxide (0.02 mole) was then added to the reaction mixture and shaking continued for two hours. After standing overnight another 0.02 equivalent of silver oxide was added and the shaking continued for three hours. After warming slightly, the solution was filtered to remove the silver iodide. The solid was washed well with warm methanol, allowing the washings to run into the original filtrate. Upon evaporating filtrate and washings there was obtained a brown oil that solidified after standing several days. The solid was taken up in warm acetone and treated with decolorizing carbon yielding an amber colored solution. Upon concentrating this solution and scratching the walls of the flask white crystals melting at 132.5-135° C. (unc) and weighing 1.5 g., (38.0 per cent) were obtained. This material was found to be readily soluble in water.

An analytical sample of the material was prepared by recrystallizing five times from acetone. The solid dissolved very slowly in hot acetone and did not crystallize readily, hence each crystallization was made by dissolving in hot acetone, evaporating to a small volume and allowing to stand for about 24 hours at 10° C. The white, minute prisms so obtained melted at 135.5-136° C. (unc) or at 134.5-135° C. (K).

Calculated for $C_{11}H_{15}N_3O_3$: N = 17.71 per cent

Found: N = 17.85 per cent

Spiro-1'-isopropylpiperidine-4',5-barbituric Acid.--A mixture of 2.96 g. (0.05 mole) of isopropylamine, 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)-barbituric acid and 350 ml. of methanol (reagent grade) was mechanically shaken in a 500-ml. glass-stoppered bottle for one hour at room temperature. At this time a small sample of the material gave a positive test for ionic iodide. Freshly prepared silver oxide (0.05 mole) was then added. The shaking was continued for 16 hours at which time an addition of an equal portion of freshly prepared and washed silver oxide was made. After 40 hours of additional shaking (the silver oxide color was apparent for approximately 20 hours) the silver iodide was removed by filtration and washed several times with hot methanol. The methanol washes were combined with the original filtrate and the alcohol removed at aspirator pressure. There remained 11.5 g. of crude product, that when recrystallized once from dry acetone weighed 6.6 g. (35.6 per cent) and melted at 141-143.5° C. (K) with decomposition. An analytical sample of this water soluble product was prepared by repeated recrystallization from dry acetone to a melting point of 143-145° C. (K).

Calculated for $C_{11}H_{17}N_3O_3$: N = 17.49 per cent

Found: N = 17.42 per cent

Spiro-1'-n-butylpiperidine-4',5-barbituric Acid.--Methanolic n-butylamine (10 ml. of a solution containing 14.6 g. per 100 ml., 0.02 moles) was added to a suspension of 8.75 g. (0.02 mole) of 5,5-bis(2-iodoethyl)barbituric acid in 100 ml of absolute methanol. After shaking the mixture at room temperature for one hour in a 250-ml glass-stoppered bottle, 0.02

mole of freshly prepared silver oxide (alkali free and alcohol washed) was introduced into the reaction mixture. Shaking was continued intermittently during the next 48 hours (three one-hour periods of shaking). Another 0.02 mole portion of silver oxide was next added with the shaking continuing for an additional one hour.

After standing for 10 hours, the silver iodide was removed by filtration and washed well with warm methanol. The combined filtrate and washings were evaporated to yield a gummy white solid, which was insoluble in ether or ethyl acetate but soluble in water, ethanol, and dioxane.

The material was recrystallized by using a minimum quantity of warm methanol to effect solution, adding ether to cloud point, and cooling slowly to 10° C. This procedure yielded 1.5 g. of pale yellow needles melting at 165-168° C. (unc). The yield, 29.8 per cent, was low due to accidental spillage during the crystallization.

An analytical sample of this material prepared by repeated recrystallizations from methanol-ether mixtures melted at 174-175° C. (K) with decomposition.

Calculated for $C_{17}H_{19}N_3O_3$: N = 16.59 per cent

Found: N = 16.66 per cent

An attempt was made to isolate a hydro iodide of this aminobarbituric acid by omitting the second addition of silver oxide. Identical quantities (0.02 mole) of starting materials were used and the mixture was shaken for one hour prior. After the addition of 0.02 mole of silver oxide, the shaking was continued (three one-hour periods during the next 32 hours). The reaction was warmed to 50° C., filtered to remove the silver iodide, the salt cake washed with 50° C. methanol, and

the filtrate and washings combined. The solution was concentrated to about 30-40 ml. then diluted to 120 ml. with dry ethyl acetate. Upon standing for several days at 0° C., 1.7 g. of white needles were obtained. This material contained no iodine and melted at 169-170° C. (unc). A mixed melting point determination proved that it was identical to the product obtained using two additions of silver oxide.

Spiro-1'-cyclohexylpiperidine-4',5-barbituric Acid.--Cyclohexylamine (4.96 g., 0.05 mole) was dissolved in 350 ml. of absolute ethanol contained in a 500-ml. glass-stoppered bottle and 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)barbituric acid was added. After shaking mechanically for one hour at room temperature (reaction occurs quite rapidly as evidenced by a positive test for iodide ion after several minutes), 0.05 mole of silver oxide was added. At the end of an additional 10-hour period of shaking, a second portion (same quantity) of silver oxide was added and shaking continued for an additional 10 hours. The silver oxide color was discharged in about 30 minutes following each addition.

The silver iodide was filtered from the mixture and washed three times by stirring with boiling absolute ethanol. The wash alcohol was combined with the original filtrate and the solvent evaporated at aspirator pressure. There remained 14 g. of a tan-colored solid. This was redissolved in a minimum quantity of absolute alcohol and a small amount of insoluble matter removed by filtration. Upon cooling, 9.0 g. (64.3 per cent) of white solid separated. This material melted at 193-195° C. (K).

An analytical sample was prepared by recrystallizations from absolute ethanol, filtering once through a mat of "purified cellulose

powder" to remove a small quantity of very finely divided particles of silver iodide.

This material melted with decomposition at 194-196° C. (K).

Calculated for $C_{14}H_{21}N_3O_3$: N = 15.01 per cent

Found: N = 14.96 per cent

Spiro-1'-phenylpiperidine-4',5-barbituric Acid.--5,5-Bis(2-iodoethyl) barbituric acid (39.5 g.; 0.09 mole) was suspended in 600 ml of absolute ethanol and 8.38 g. (0.09 mole) of freshly distilled aniline was added. The resulting mixture was placed in a 500 ml. glass-stoppered bottle and mechanically shaken in the dark at room temperature for 78 hours.

Silver oxide (0.09 mole) was added and the shaking continued for 167 hours. The dark color of the silver oxide was rapidly discharged. Another equal portion of silver oxide was added and the shaking continued for 24 hours. Again the dark color was rapidly discharged. The mixture was filtered and the silver iodide washed with acetone at room temperature. The filtrate and washings were combined and the solvent removed under reduced pressure. The resulting gummy mass could not be made to yield a crystalline product. This material was set aside and not examined further.

The washed filter cake was stirred twice with 300 ml. of hot water and refiltered. Upon cooling the clear filtrate, 8 g. of crude iodine-free solid melting near 200° C. (unc) was obtained.

Further washing of the cake with hot water and cooling the filtrate yielded only an insignificant amount of material. The total 8 g. of crude product represents a 32 per cent yield. Recrystallization from water to a melting point of 200-202° C. yielded only 4 g.

An analytical sample was prepared by recrystallizing once from methanol (50 per cent loss) and four times from water. This sample melted at 202-202.5° C. (K) with decomposition.

Calculated for $C_{14}H_{15}N_3O_3$: N = 15.38 per cent

Found: N = 15.18 per cent

Spiro-1'-phenylpiperidine was found to be only slightly soluble in water; 0.165 g. dissolving in 100 g. of water at 26.5° C. A previous preparation of this spiro-amino barbituric acid had resulted in a 64 per cent yield, however, this yield could not be duplicated in subsequent runs.

Spiro-1'-benzylpiperidine-4',5-barbituric Acid.--Ten ml. of an ethanolic solution of benzyl amine containing 2.14 g. of the amine was added to a suspension of 8.75 g. (0.02 mole) of 5,5-bis(2-iodoethyl)barbituric acid in 100 ml. of absolute ethanol. After shaking the reaction mixture for one hour 0.02 mole of freshly prepared, alkali free silver oxide was added, following which the whole was shaken intermittently (three one hour periods) during the next 45 hours. Then a second 0.02 mole portion of silver oxide was added and shaking continued for one more hour. The mixture was warmed to 60° C. and filtered. The cake of silver iodide was washed three times by stirring with enough hot ethanol to make a thin paste and filtered. Evaporation of the filtrate and washings to about 50 ml. followed by cooling overnight at 10° C. gave a white crystalline powder (3.3 g.; 52.7 per cent) which melted at 164-165° C. An analytical sample was prepared by repeated recrystallizations from ethanol-ethyl acetate mixture, washing the crystals each time with ethyl acetate. The product melted with decomposition at 172.5-173.5° C. (unc) or at 173-174° C. (K).

Calculated for $C_{15}H_{17}N_3O_3$: N = 14.63 per cent

Found: N = 14.61 per cent

Several previous attempts to prepare this particular compound were without success. All the early attempts were made using more vigorous reaction conditions. Thus, when 4.36 g. (0.01 mole) of 5,5-bis(2-iodoethyl)barbituric acid was added to 3.21 g. (0.03 mole) of benzylamine in 20 ml. of dioxane and warmed, the pale yellow solution rapidly became blood red. After about five minutes the red color faded and the solution was again pale yellow. Gradually the solution again became quite red. This solution was refluxed for 12 hours, then the solvent was distilled under reduced pressure. There remained 8.1 g. of dark liquid which was treated with water and 0.01 mole of freshly prepared silver oxide. The silver iodide was filter from the mixture and the filtrate frozen. Upon thawing and filtering, 0.15 g. of the white needles was obtained. After being recrystallized from toluene this material melted at 148-149° C. (unc). The analysis did not correspond to that calculated for the expected product (C = 62.70; H = 5.97; N = 14.63 per cent). It is believed that the small amount of material isolated is benzylurea (melting point 147-148° C.), resulting from too harsh reaction conditions.

Calculated for benzylurea, $C_8H_{10}N_2O$: C = 63.97; H = 6.70; N = 18.66 per cent

Found: C = 63.95; H = 6.71; N = 18.31 per cent

A very small quantity of the same solid was isolated when benzylamine and 5,5-bis(2-iodoethyl)barbituric acid were refluxed in n-butanol containing an excess of potassium carbonate.

In a similar attempted preparation using the bicarbonate rather than the carbonate in refluxing n-butanol, a partly crystalline, oily material was obtained. Treatment with hot toluene removed the oily portion which could not be made to crystallize. The solid remaining from the toluene treatment was water soluble and contained ionic iodine. When recrystallized from ethanol, the solid melted at 192-192.5° C. (unc) with evolution of a gas. The melt, after solidifying, melted at 123-128° C. (unc). Gravametric analysis (weighed as silver iodide) gave 33.87 and 33.92 per cent iodine. This compound was not identified because of the very small quantity obtained, 0.8 g. from 4.36 g. of 5,5-bis(2-iodoethyl) barbituric acid.

Spiro-1'-o-tolypiperidine-4',5-barbituric Acid.--The 5,5-bis(2-iodoethyl) barbituric acid (21.8 g.; 0.05 mole) was added to 5.36 g. (0.05 mole) of o-toluidine in 175 ml. of purified methanol and the resulting mixture shaken at room temperature for 5.75 hours. Silver oxide (from 0.05 mole of silver nitrate) was prepared, washed with methanol and added to the reaction mixture. Only very slow conversion of the silver oxide to the iodide occurred--four days being required to discharge the dark color. A second portion of silver oxide was added and the shaking continued for three days, after which warming to 50° C. and filtering removed the silver iodide. The solid portion was washed twice with 50 ml. of hot (50° C.) methanol, the washings being allowed to mix with the original filtrate. Treatment of the dark solution with activated carbon followed by filtration, and evaporation of the resulting cherry red filtrate to 50 ml. by means of reduced pressure, gave 2.5 g. of white solid. An additional

1.7 g. of product was obtained by adding ethyl acetate to the filtrate and again cooling. The total yield was 4.2 g., or 29.3 per cent.

An analytical sample was prepared by recrystallizing from methanol. This material melted with decomposition at 178-179° C. (K).

Calculated for $C_{15}H_{17}N_3O_3$: N = 14.63 per cent

Found: N = 14.30 per cent

Spiro-1'-p-tolypiperidine-4',5-barbituric Acid.--To 2.18 g. (0.025 mole) of p-toluidine in 175 ml. of absolute ethanol was added 10.9 g. (0.05 mole) of 5,5-bis(2-iodoethyl)barbituric acid. The resulting mixture, contained in a 250-ml. glass-stoppered bottle, was mechanically shaken at room temperature for eight hours. Freshly prepared silver oxide (0.025 mole) was then added. Shaking was continued for eight hours during which time the silver oxide color was discharged and the mixture in the bottle became rather gel-like. Another equal portion of silver oxide was introduced and the shaking continued for 24 hours. As the silver oxide color was discharged, the contents of the reaction bottle became more fluid.

The silver iodide was removed by filtration and washed well with hot ethanol, the wash alcohol being collected with the original filtrate. Removal of the solvent at reduced pressure left 4.5 g. of brown solid that was washed well with hot ethyl acetate to remove the colored matter. The crude yield of 3.8 g. was 52.9 per cent of the theoretical. This product did not crystallize readily from any of the 15 common solvents tried. It could be recrystallized slowly from n-butanol, over 24 hours at 0° C. being required for crystallization. The pure compound melted at 157-158° C. (K).

Calculated for $C_{15}H_{17}N_3O_3$: N = 14.63 per cent

Found: N = 14.68 per cent

A previous preparation on a 0.05 molar scale was made identical to the above. However, the crude product was recrystallized from Reagent Grade "Xylol." The material was not readily soluble cold and crystallized rather rapidly when the solution was cooled. The material so obtained was found to melt at 180.5° C. (K). The analysis indicated that the material contained 12.34 per cent nitrogen. This value corresponds to a value that would result if the desired compound had crystallized with one-half mole of xylene;

Calculated for $C_{15}H_{17}N_3O_3 \cdot 1/2\ C_8H_{10}$: N = 12.34 per cent

No weight loss could be effected by heating a sample in a drying pistol at 82° C. and 1-mm. pressure for 18 hours. When a sample of the spiro-1'-p-tolylpiperidine melting at 157-158° C. (K) was repeatedly recrystallized from xylene the melting point was changed to that of the compound that analyzed for 12.34 per cent nitrogen. Since the spiro-amino barbituric acids are known to decompose upon heating, there is some doubt if the compound recrystallized from "xylol" is a true hemi-solvate or a degradation product of the barbituric acid. The infrared curve, however, indicates a structure similar to the spiro-1'-p-tolylpiperidine-4',5-barbituric acid. (See Appendix.)

Attempted Preparation of Spiro-1'-m-tolypiperidine-4',5-barbituric Acid.--A mixture of three g. (0.028 mole) of m-toluidine and 12.21 g. (0.028 mole) of 5,5-bis(2-iodoethyl)barbituric acid in 150 ml. of absolute ethanol was shaken for 14 hours at room temperature. Freshly prepared silver oxide (from 0.028 mole of silver nitrate) was added and shaking continued

for 3.5 days. At this time the solid portion appeared to be silver iodide; however, the liquid portion was quite dark, making it difficult to be certain. Another portion of silver oxide was added and the shaking continued for 3.5 days. The solid was filtered and washed twice with 50 ml. of boiling ethanol. The washings and filtrate (dark purple) were combined and treated with carbon to yield a dark amber solution. Removal of the solvent by means of reduced pressure yielded a red gummy mass containing a small quantity of solid substance. The entire material was taken up in 20 ml. of hot ethanol and treated with 30 ml. of ethyl acetate. Upon chilling for several weeks, there was deposited one g. of white solid (12.4 per cent yield) that melted at approximately 160° C. This material was not further purified.

Spiro-1'-(2-phenylethyl)piperidine-4,'5-barbituric Acid.--To a suspension of 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)barbituric acid in 300 ml. of absolute ethanol was added 6.06 g. (0.05 mole) of phenethyl amine This mixture was shaken for eight hours and a portion of freshly prepared silver oxide (from 8.5 g., 0.05 mole, of silver nitrate and a slight excess of 20 per cent sodium hydroxide) was added. The silver oxide color was no longer apparent after about two hours. A second portion of silver oxide was added and the shaking continued for four hours. Filtration removed the silver iodide and concentration of the filtrate to a volume of 50 ml., (room temperature and reduced pressure) resulted in the crystallization of 3.2 g. of crude product. Washing the silver iodide by stirring with 150 ml. of boiling ethanol, filtering and cooling the filtrate resulted in an additional 8.5 g. of solid melting at 160.5-162.5° C (K). The total yield of crude product was 11.7 g. or 77.7 per cent of the theoretical.

Recrystallization was effected from absolute ethanol to yield a pure product that melted with some decomposition at 185-187° C. (K).

Calculated for $C_{16}H_{19}N_3O_3$: N = 13.94 per cent

Found: N = 13.75 per cent

The solubility of spiro-1'-(2-phenylethyl)piperidine-4',5-barbituric acid in water at 26.5° C was found to be 1.13 g. per 100 g. of water.

Attempted Preparation of Spiro-1'-(trishydroxymethyl)methylpiperidine-4',5-barbituric Acid.--A mixture of 6.06 g. (0.05 mole) of tris(hydroxymethyl)aminomethane (sample from Commercial Solvents Corporation), 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)barbituric acid and 150 ml. of purified methanol was shaken for six hours at room temperature. Freshly prepared silver oxide (from 0.1 mole of silver nitrate) was added and shaking continued for ten hours. The silver iodide was removed by filtering and washed well with methanol. The filtrate and washings were combined and reduced in volume (aspirator pressure) until a solid began to separate. Upon cooling, 1.5 g. of pink solid were obtained. Further removal of the solvent left a thick oil that was finally obtained as a white solid by crystallizing from n-butanol. The white hygroscopic solid weighed 1.8 g. This material was not purified for analysis. It appeared to decompose upon standing, becoming dark in color and semisolid.

Attempted Preparation of Spiro-1'-hydroxypiperidine-4',5-barbituric Acid.--To a mixture of 200 ml. of absolute ethanol and 1.74 g. (0.025 mole) of hydroxylamine hydrochloride was added 0.025 mole of methanolic potassium hydroxide (4.3 N). When no more potassium chloride separated, solid 5,5-bis(2-iodoethyl)barbituric acid (10.9 g.; 0.025 mole) was added.

After shaking for 1.5 hours, 0.025 mole of silver oxide (freshly prepared and washed with absolute ethanol) was added. Shaking was continued for two days and a second portion of silver oxide added with continued shaking for an additional 48 hours. The mixture was filtered and the solid material washed well with boiling ethanol. Since the filtrate was found to contain iodide ions it was treated with a third portion (0.025 mole) of silver oxide. After a five hour shaking period, the solid was removed to give a clear iodine free solution. Evaporation of the solvent left five g. of a hygroscopic solid. Recrystallization was effected from n-butanol but the recovery was poor, 1.8 g. This crude material was not purified for analysis.

Attempted Preparation of Spiro-1'-(2-carboxymethyl)-piperidine-4',5-barbituric Acid.--A mixture of 375 ml. of dioxane, 3.75 g. (0.05 mole) of glycine and 21.8 g. (0.05 mole) of 5,5-bis(2-iodoethyl)barbituric acid, contained in a 500-ml. glass-stoppered bottle, was shaken at room temperature for eight hours. Freshly prepared, alcohol-washed, silver oxide (0.05 mole) was added to the reaction mixture with shaking continuing for 48 hours. The brown color of the silver oxide was not discharged as in the reactions with the amines, the reaction mixture becoming almost black. A second portion of silver oxide was added and shaking continued for an additional 48 hours. The black solid was filtered from the dioxane, and washed with warm dioxane. The filtrate and washings were evaporated to dryness at reduced pressure, and there remained 12 g. of a pale yellow solid that contained non-ionic iodine. Recrystallization of this solid was effected once from a dioxane-water mixture and once from ethyl acetate. The resulting white fluffy needles melted with decomposition at

168-173° C. (K). Analyses for iodine were made by warming samples with benzylamine in a small quantity of ethanol to liberate the iodine as iodide followed by titrating by the Volhard method. The analysis, 33.7 per cent of iodine, indicated that the glycine had reacted with the 5,5-bis(2-iodoethyl)barbituric acid to replace only one iodine atom. The calculated iodine content for the structure that would result by such a reaction is 33.13 per cent. Based on the assumption that the compound isolated was 5-(2-iodoethyl)-5-(2-carboxymethylaminoethyl)barbituric acid, the crude product represented a 62.6 per cent yield.

A portion of the iodine-containing product (2.45 g., 0.0064 mole) was dissolved in 20 ml. of pyridine and heated to boiling. A test sample was removed and found to contain ionic iodine. The mixture was cooled to room temperature and the silver oxide prepared from 1.07 g. (0.0062 mole) of silver nitrate was added after adding 40 ml. of absolute ethanol and several granules of alumina. The mixture was shaken overnight. Following removal of the solvents by warming under reduced pressure, the remaining solid residue was extracted three times with 150 ml. of boiling acetone. The filtered extract was reduced in volume to about 75 ml. and cooled. Crystallization occurred but upon standing the solid material moved out of the solvent and coated the walls of the flask as a pale yellow crust. This solid was removed and recrystallized from acetone filtering as soon as crystallization occurred. This pale yellow iodine-free material (0.4 g.) was not purified further. Its infrared spectra was unlike that of spiro-barbituric acids. When heated in the melting point apparatus to about 160-200° C, it sublimed; the sublimate melted at 228-230° C. (K). Since this value is near that reported for

glycine (232-236° C. dec.), a mixed melting point determination was made. There was no depression; however, the mixture decomposed more pronouncedly than did the suspected barbituric acid. In addition, the suspected barbituric acid did not give a positive ninhydrin test for an amino acid. In a control under identical conditions, the glycine gave a deep blue positive test.

Attempted Preparation of 5,5-Bis(dimethylaminoethyl)barbituric Acid.--To nine g. of 5,5-bis(2-iodoethyl)barbituric acid and 100 ml. of reagent grade methanol, was added 15 g. (an excess) of dimethylamine. The mixture was allowed to stand at room temperature for four days. Upon cooling to 10° C. and filtering, there resulted 3.5 g. (62.8 per cent) of white needles. The material melted with decomposition at about 170° C. (unc). An analytical sample prepared by recrystallizations from methanol did not give the expected nitrogen analysis.

Calculated for $C_{12}H_{22}N_4O_3$: N = 20.73 per cent

Found: N = 16.38 per cent

No explanation for these results is apparent at this time.

A repeat preparation was made using 21.8 g. (0.05 mole) of the 5,5-bis(2-iodoethyl)barbituric acid, 9.5 g. (0.21 mole) of dimethylamine and 200 ml. of methanol. The amount of amine used in this preparation is five per cent greater than the amount required for reaction. The product isolated (10 g., 14.7 per cent) appeared to be identical to that obtained previously. However, repeated recrystallizations from methanol were made, with little change in the melting point, and the nitrogen analysis was repeated. The nitrogen content was found to be 16.72 per cent. This compound was not identified. A di-alcoholate of the desired

structure would have a nitrogen content of 16.75 per cent. The infrared spectra, however, was quite different from that of known barbituric acids, and no weight loss could be effected by drying.

Preparation of Spirotetrahydropyran-4',5-iminobarbituric Acid.--Sodium isopropoxide was prepared from three liters of isopropyl alcohol and 69 g. (3 g. at.) of sodium. To this solution was added 122 g. (one mole) of guanidine nitrate. After stirring for 15 minutes, 230 g. (one mole) of diethyl tetrahydropyran-4,4-dicarboxylate was added and the resulting mixture refluxed with stirring for 48 hours. Hydrogen chloride gas was passed into the chilled (5° C.) mixture until a sample, when mixed with water, gave a definite acidic test. The salts were removed by centrifuging, subjected to reduced pressure to remove adhering alcohol and hydrogen chloride, and then shaken vigorously with two liters of cold (5° C.) water. The solid was separated by filtration. Upon neutralizing the aqueous filtrate with ammonium hydroxide, no imino-barbituric acid precipitated. The solid portion which was dried free of water at reduced pressure was found to be organic and contained both nitrate and chloride ions. Therefore, it may be a mixed salt of the desired product. The material was found to be essentially insoluble in water and a variety of organic solvents. It was soluble in hydrochloric acid and sodium hydroxide but only slightly soluble in cold ammonium hydroxide. A saturated aqueous solution had a pH of 1.5. Assuming it to be a mixture of equal parts of the nitric acid and hydrochloric acid salts), a yield of 36 per cent (87 g.) was obtained.

After placing this material in a two-liter bottle with one liter of cold water, 500 g. of ice, and 200 ml. of concentrated ammonium

hydroxide, the mixture was rolled in the bottle on a ball mill until the ice had melted. While still cold the solid was separated on a filter and washed with cold water until the wash liquid contained no chloride ion. The white solid that remained on the filter melted at 318-327° C. (K) and was found to be organic and to contain no chloride or nitrate. Since it appeared to sublime slightly just below its melting point, attempts were made to purify the solid by sublimation at one mm. pressure. The results obtained were inconsistent and there was evidence that decomposition occurred at the high temperature required (about 250° C).

Although the high melting point may seem unusual for an organic material, it should be noted other spiro-amino barbituric acids are reported that do not melt below 300° C.[40]

The product was essentially insoluble in water (an aqueous solution having a pH of 6.3) and was soluble in both dilute hydrochloric acid and dilute sodium hydroxide. Attempts to reprecipitate the compound from either acidic or basic solutions by neutralizations were unsuccessful.

The solid was insoluble in most organic solvents, but recrystallization of a small sample was effected from "Cellosolve"; approximately 500 ml. per g. being required.

Calculated for $C_8H_{11}N_3O_3$: N = 21.31 per cent

Found: N = 20.77 per cent

Spirotetrahydropyran-4',5'-thiobarbituric Acid.--To 9.2 g. (0.4 g. at.) of sodium "dissolved" in one liter of t-butyl alcohol was added 20.5 g. (0.4 mole) of thiourea followed by 46 g. (0.2 mole) of diethyl tetrahydropyran-4,4-dicarboxylate and the whole refluxed for 24 hours. A small

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[40] A. W. Dox and L. Yoder, J. Am. Chem. Soc., 43, 677, 1366 (1921).

portion of the reaction mixture was removed from the flask, cooled, and filtered. The insoluble salts thus obtained were added to an excess of cold (0° C.) hydrochloric acid. The crystalline product was recrystallized once from water, once from a dioxane-water mixture, and once from isopropyl alcohol. The glistening yellow plates (3 g.) melted at 217.5-220° C. (unc).

The major portion of the reaction mixture was cooled to 0° C. and treated with excess gaseous hydrogen bromide. After shaking vigorously the mixture was allowed to stand for 48 hours at 10° C. The solution was allowed to warm sufficiently to thaw the t-butyl alcohol solvent, and then the solid was collected by filtering. Treatment of the solid with 750 ml. of hot water followed by filtration left most of the thiobarbituric acid undissolved. The small amount that dissolved was recovered by cooling the filtrate. The combined solids were treated with 300 ml. of isopropyl alcohol containing enough dioxane to effect solution at the boiling point; decolorizing carbon was added and upon filtering and cooling there was obtained 20 g. of light yellow needles that melted at 217-220° C. (unc). A mixed melting point with a portion of the three g. of material obtained previously indicated the two solids were identical. Since the melting point was about the same as the oxygen analog, a mixed melting point was determined. There was a depression to 183-195° C. The total yield from this preparation was 23 g. or 53.7 per cent of the theoretical amount.

An analytical sample was prepared by recrystallizing from water then from isopropyl alcohol. This sample was stored in a vacuum over anhydrous calcium sulfate and magnesium chloride. After about three days

it was noticed that the surface was darker yellow than the remainder. After several weeks the entire sample was the same darker yellow. (This may indicate decomposition or, possibly, a loss of solvent. The oxygen analog is known to crystallize with one mole of water.)

Calculated for $C_8H_{10}N_2O_3S$: N = 13.08 per cent

Found: N = 12.90 per cent

Stability of Spirotetrahydropyran-4',5-thiobarbituric Acid in Basic Medium.--One g. of the thiobarbituric acid was added to 0.5 g. of sodium hydroxide in 10 ml. of water. The resulting solution was allowed to stand for five minutes at room temperature. Carbon dioxide was passed into the solution until it was saturated. No solid separated even after standing at 10° C. for several days. This indicated that no significant amount of 5,5-substituted barbituric acid remained.[41]

When one g. of the thiobarbituric acid was allowed to stand for 48 hours at 27° C. with a solution of 0.5 g. of sodium hydroxide in 10 ml. of water, the only material that could be isolated, upon acidification, was tetrahydropyran-4,4-dicarboxylic acid. This case of hydrolysis is similar to that found for the oxygen analog.

Stability of Spirotetrahydropyran-4',5-thiobarbituric Acid in Acidic Medium.--That the compound is not extremely unstable in acid solution is apparent by the method of isolating the major portions during the preparation, i.e., the first water-wash undoubtedly contained amounts of hydrobromic acid, yet upon cooling this wash, unchanged thiobarbituric acid was obtained.

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[41] E. M. van Heyningen, J. Am. Chem. Soc., 76, 2241 (1954).

Attempted Preparation of 5,5-Bis(2-iodoethyl)thiobarbituric Acid.--A mixture of 4.28 g. (0.02 mole) of spirotetrahydropyran-4',5-thiobarbituric acid, 13.5 g. potassium iodide (0.08 mole) and 30.9 g. of 95 per cent phosphoric acid was placed in a 125-ml. three-necked flask and heated to 120° C. During the heating (10 hours) the flask and contents were shaken vigorously by clamping a ring stand holding the heating mantle, flask, condenser, and thermometer in a laboratory shaker.

After about one hour of shaking, a pronounced odor of hydrogen sulfide was apparent. The reaction mixture was poured onto crushed ice while warm. No product could be separated from the black tarry reaction mixture.

Infrared Spectra.--Samples of materials that were crystalline were compressed in potassium bromide discs and the infrared spectra were recorded from these discs using a Perkin-Elmer Model 21 recording infrared spectrophotometer.[42] The discs were prepared by weighing 0.001 g. of the solid and adding dry, finely pulverized (325-mesh screen) potassium bromide to make a total weight of 0.1 g. This 0.1 g. sample was intimately mixed by grinding in an agate mortar. The grinding insured that the organic material was in a finely divided state and uniformly distributed throughout the potassium bromide. The total sample was compressed into a 1/2-inch diameter disc, using about 35,000 pounds per square inch pressure, in a briqueting press (Applied Research Laboratories).

The intensity of the reference beam of the spectrophotometer was adjusted by inserting fine wire screens into the path of the beam. By such an adjustment, and with the instrument controls, it was possible to

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[42] M. M. Stimson and M. J. O'Donnel, J. Am. Chem. Soc., 74, 1805 (1952).

record the entire spectra (2-15 microns) so that the curves fell between zero and 100 per cent transmission.

The spectra of the liquid compounds were determined in the usual manner in a 0.02 mm. cell without solvent. The infrared spectra of the new spiro-amino barbituric acids, and some related compounds, are included in the Appendix (Figures 19 through 46).

Ultraviolet Spectra.--The ultraviolet absorption spectra were determined using a Beckman DK-2 recording spectrophotometer. The spectra of the following compounds were examined as aqueous solutions and in aqueous basic solutions:

5,5-diethylbarbituric acid

Spirocyclopentane-1',5-barbituric acid

Spirocyclohexane-1',5-barbituric acid

Spirotetrahydropyran-4',5-barbituric acid

Spirotetrahydropyran-4',5-thiobarbituric acid

Spiro-1'-methylpiperidine-4',5-barbituric acid.

All spectra were run on solutions with a concentration of 10^{-4} molar in barbituric acid. The solutions were prepared as described in the following section on basic hydrolysis. After mixing the basic solution the region from 220 to 340 mμ was scanned at the fastest rate possible in order that the absorption peaks could be located before hydrolysis of the salts had occurred. In the cases where rapid hydrolysis was known to occur this region was scanned within 1.5 to 2.0 minutes after mixing.

The absorption of the spiro-1'-methylpiperidine-4',5-barbituric acid was also recorded in hydrochloric acid solutions, 1.057 normal and

10.5 normal in mineral acid and 10^{-4} molar in barbituric acid. The absorption bands for these materials are summarized in Table 3, Chapter II.

A reproduction of the absorption curves of 5,5-diethylbarbituric acid, which are typical of 5,5-dialkylbarbituric acids is included in the Appendix (Figure 47). Also reproduced, as an example of the type curves characteristic of spiro-barbituric acids, are the curves obtained with spirotetrahydropyran-4',5-barbituric acid (Figure 48). A third reproduction, that of the curves obtained with spiro-1'-methylpiperidine-4',5-barbituric acid (Figure 49), is also included in the Appendix.

Basic Hydrolysis of Some Spiro-barbituric Acids.--In order to check the feasibility of determining rates of basic hydrolysis of the barbituric acids by ultraviolet light absorption and to obtain information concerning the relative rates of basic hydrolysis of spiro-barbituric acids, some preliminary studies have been made.

a. Apparatus and Materials.

A Beckman Model DK-2 Recording Spectrophotometer was used throughout the studies. The cell compartment cover was replaced by an improvised thermostated cover. Temperature control in the cell compartment was accomplished by circulating thermostated water (from a Fisher Scientific Company constant temperature circulating pump, ± 0.05° F.) through the cell cover. The cell compartment was insulated as well as possible with wool felt and "kaolin wool". Good temperature control could be maintained when the operating temperature was above 35° C., but at lower temperatures the heat generated by the hydrogen lamp and particularly by the mirror rotating motor of the spectrophotometer caused an upward drift

in temperature. This drift was sufficiently slow, however, that when hydrolyses which were essentially complete in less than 20 minutes were being run, no detectable rise in temperature was noted. Above 35° C. no temperature rise was apparent for periods as long as 12-14 hours provided that temperature equilibrium was established with the light source on and with the mirror rotator motor operating.

Carbonate free stock sodium hydroxide solution was prepared from reagent grade pellets and distilled water that had been passed through a mixed bed ion exchange resin. This stock solution was stored in a polyethylene bottle until used.

Sodium carbonate-sodium bicarbonate buffer solution was made using 0.025 molar sodium carbonate (C.P.) and 0.25 molar sodium bicarbonate (C.P.). The pH of such a buffer as measured by Bates, et al,[43] is 9.91 at 38° C. The measured pH, using standard electrodes in a Model G Beckman pH meter without correction, was 9.81 at 28° C.

Stock solutions (10^{-3} molar) of the barbituric acids were prepared by weighing analytically pure materials to ± 2 micrograms and dissolving in 100 ml. of deionized water. The stability of these solutions was found to be excellent. This was determined by preparing a solution 10^{-4} molar in barbituric acid and 4 molar in sodium hydroxide from the stock solutions, plotting the rate of hydrolyses, followed spectrophotometrically (see below) and extrapolating to zero time. After allowing the stock solutions of the acids to stand at room temperature for a period

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[43] R. G. Bates, G. D. Pinching, and E. R. Smith, J. Research Natl. Bur. Standards, 45, 518 (1950).

of time ranging from one to two months the process was repeated and no detectable change in initial concentration was apparent.

b. Procedure for Hydrolysis Rate Determinations.

From the stock solution of sodium hydroxide 100 ml. of base of the required strength was prepared and thermostated at the temperature selected for the determination. This diluted sodium hydroxide was used in the reference cell of the spectrophotometer and to zero the instrument prior to the determination.

The stock solution of the particular barbituric acid (10^{-3} molar) was thermostated at the desired temperature, as was 90 ml. of sodium hydroxide of the required strength. When temperature equilibrium was established, 10 ml. of the stock acid solution was pipetted into the base. Simultaneously a stopwatch was started when the rate of hydrolysis was anticipated to be rapid, or, in the case of slower reactions, the exact time of mixing was noted. The solution was manually mixed as rapidly as possible and transferred to a 1.000 cm. quartz absorption cell which had previously been equilibrated at the same temperature by means of the thermostated cell compartment. (The cell was flushed several times with the reaction mixture to insure that a representative sample was being measured.) Measurements of the optical density were then recorded at the predetermined wave length. (i.e. the wavelength of maximum absorption under the particular reaction conditions.)

For those reactions which proceeded rapidly, the cell was then used as the reaction vessel and the time drive mechanism was started. The time after mixing was marked on the chart paper at the point the plotting began. The curve so obtained consisted essentially of an

infinite number of points. (Prior to obtaining the time drive accessory, points were marked at 15 second intervals by moving the pen manually at a selected fixed wavelength.)

For those hydrolyses which proceeded rather slowly (i.e., not essentially completed in 20 to 30 minutes), the reactions were run in a thermostated water bath in 100 ml. volumetric flasks. Samples were drawn periodically and optical densities were determined. In these determinations the cell compartment was also thermostated at the reaction bath temperature.

In all cases studied the base was present in essentially a constant amount throughout the rate run. This was accomplished either by using a large excess of sodium hydroxide or in the case of the hydrolysis of the monoionic species, by means of a buffered solution. In all cases, pseudo-first-order rates were obtained. Since the curves that were drawn by the instrument were plots of optical density versus time with the values of the optical density falling to zero at "infinite" time, the most convenient method of determining the rates was to transfer the data directly to semi-log graph paper and determine the slope of the resulting straight line.

The data obtained from these determinations have been summarized in Chapter II.

As might be expected some variation in rate determinations were apparent with the very rapid rates; however, these errors were not exceedingly large. A semi-log plot of several individual determinations, one of a rapid hydrolysis, that of spirotetrahydropyran-4',5-barbituric acid, is included in the Appendix (Figure 50). Since the slopes of the

lines are fairly consistant the errors are more probably caused by dilution errors which resulted from the necessary rapid preparation of the samples.

The data obtained from hydrolysis runs for all the other compounds studied had no greater deviation between runs that that of the example illustrated.

CHAPTER IV

CONCLUSIONS

Two methods that appeared to be suitable for preparing spiro-amino barbituric acids have been investigated, not extensively, without success.

A satisfactory procedure for preparing the desired nitrogen containing spiro-barbituric acids has been developed.

Infrared spectra have been recorded for the new spiro-amino barbituric acids, as well as for some related compounds, intermediates and by-products.

An interpretation of the infrared spectra of several types of barbituric acids has warranted the assignment of a zwitterionic structure for the spiro-amino barbituric acids.

Marked differences, not entirely explained, in the ultraviolet spectra of 5,5-dialkylbarbituric acids, some spiro-barbituric acid, spiro-1'-methylpiperidine-4',5-barbituric acid and basic aqueous solutions of these materials were found.

The ultraviolet absorption of spiro-1'-methylpiperidine-4',5-barbituric acid in deionized water and in a solution buffered to a pH of 7.0 was found to be similar to the absorption attributed to a monovalent 5,5-disubstituted barbituric acid anion.

An ultraviolet spectrophotometric method of following the rate of basic hydrolysis of certain derivatives of barbituric acids has been shown to be feasible.

The relative rates of hydrolysis of several types of spiro-barbituric acids and 5,5-diethylbarbituric acid have been determined in a strongly basic solution and significant differences in the rates were found; spirocyclopentane-1',5-barbituric acid, spirocyclohexane-1',5-barbituric acid, and spirotetrahydropyran-4',5-barbituric acid were found to hydrolyze rapidly in an aqueous base; spiro-1'-methylpiperidine-4',5-barbituric acid and 5,5-diethylbarbituric acid, in contrast, hydrolyzed only slowly under comparable conditions.

CHAPTER V

RECOMMENDATIONS

It is felt that certain additional spiro-amino barbituric acids should be synthesized, particularly compounds which are substituted in the piperidine ring. These compounds would be of interest because of the known increased physiological activity of similarly substituted spirocarbocyclicbarbituric acids over the unsubstituted compounds.[44] These could probably be prepared by the successful procedure developed during this work.

The structures that would result from the successful condensations of amino acids with 5,5-bis(2-iodoethyl)-barbituric acid would also be of interest. One such attempt with glycine has been made but has not been vigorously pursued.

Additional investigations of the hydrolysis of spiro-barbituric acids should be made. The investigations reported herein were of a preliminary nature to establish that a particular method might be applicable. Since ultraviolet absorption was found to be convenient for following the rates of basic hydrolysis it is suggested that method be utilized. It is further suggested that basic hydrolysis rates be studied in solutions buffered to pH values that would give rise to the monovalent barbituric acid ion. The use of buffered solutions would permit the reactions to be studied at an essentially constant hydroxide ion concentration. It should be possible to operate over a moderately wide pH range and still maintain the

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[44] A. C. Cope, P. Kovacic, and M. Burg, J. Am. Chem. Soc., 71, 3658 (1949).

monovalent species without the formation of a significant amount of the divalent ion. This use of reaction conditions where only one ionic species is present would have the advantage of a less complex reaction. The buffered solutions could be prepared in a manner that would result in a constant ionic strength for reaction at different hydroxide ion concentrations. By the use of constant initial concentrations of the barbituric acid derivative and making runs at varying hydroxide ion concentrations, it would be possible to determine the rate dependence upon hydroxide ion concentration.

In view of the rapid rate of hydrolysis observed with certain spirobarbituric acids and the low level of physiological activity associated with these compounds, it would be well to compare the rates of hydrolysis of various 5,5-dialkylbarbituric acids for which there is sufficient information available concerning the level and duration of activity. The data obtained from such a study would establish if a relationship exists between the hydrolytic stability and physiological activity of these compounds.

If the mechanism of hydrolysis of derivatives of barbituric acid proves to be similar to that of β-diketones and related materials, the relative strengths of the acids would be of importance, particularly under hydrolysis conditions where the divalent ion species is present. It would be well, therefore, to determine the ionization constants for the spirobarbituric acids as a complement to the hydrolysis investigations. In buffered solutions where monovalent anions are present, the acid strengths would not be so important since the monovalent species as such exists with a position available for attack by hydroxide ion.

APPENDIX

Figure 19. 5,5-Diethylbarbituric Acid.

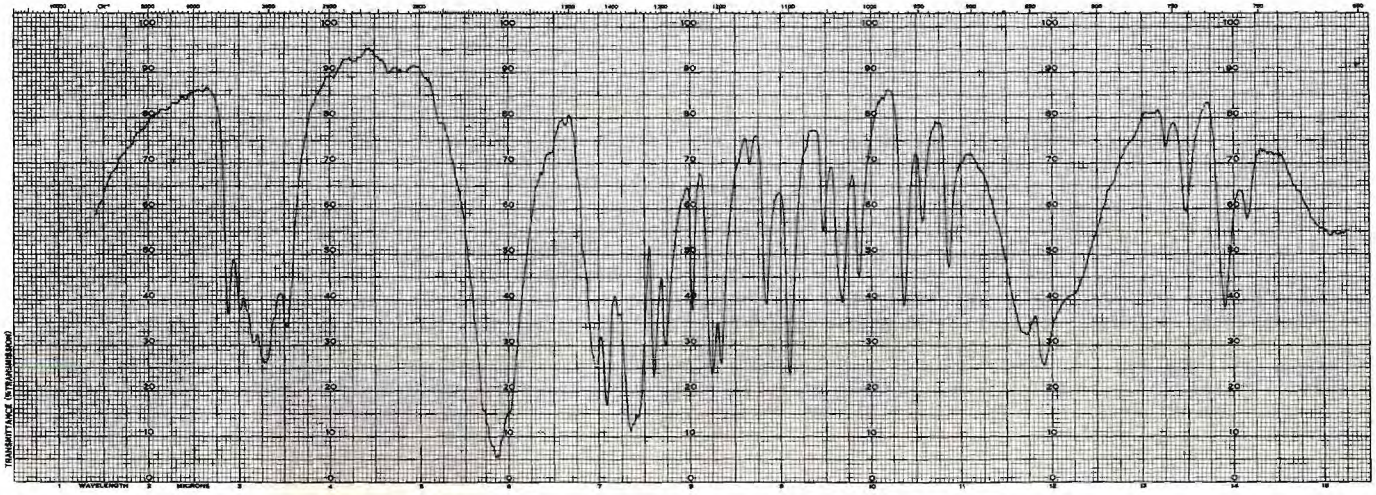

Figure 20. Spirotetrahydropyran-4',5-barbituric Acid.

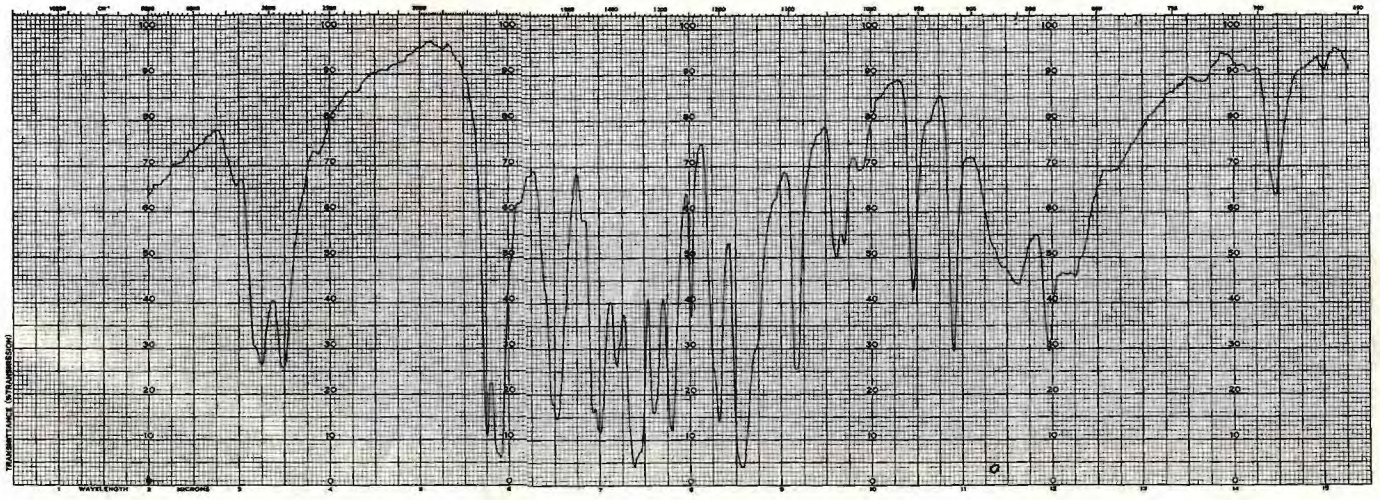

Figure 21. Spirotetrahydropyran-4',5-thiobarbituric Acid.

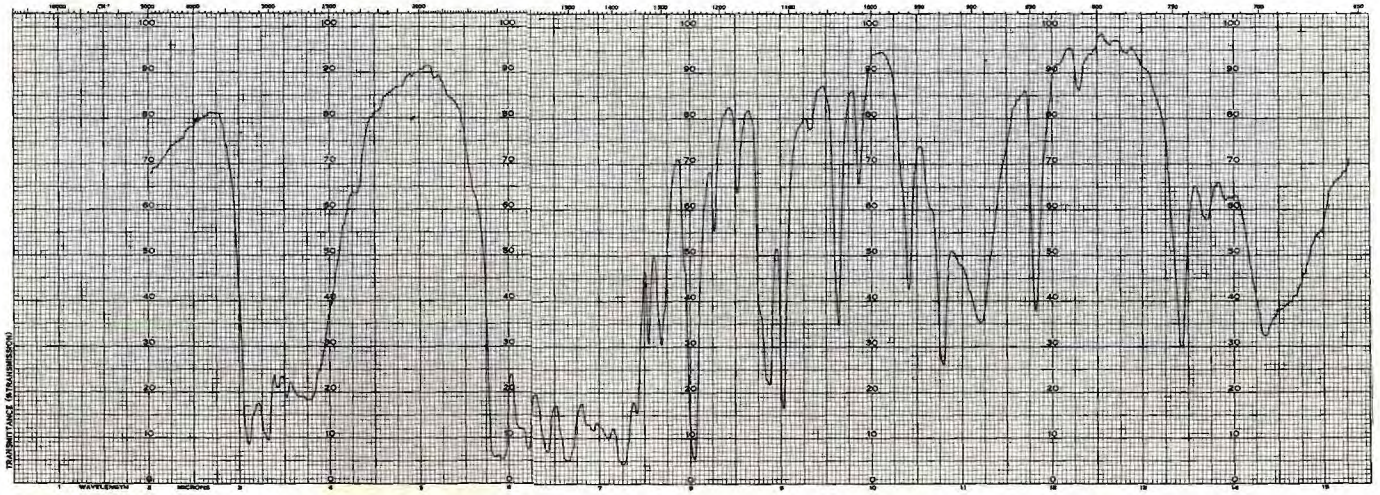

Figure 22. Spirotetrahydropyran-4',5-iminobarbituric Acid.

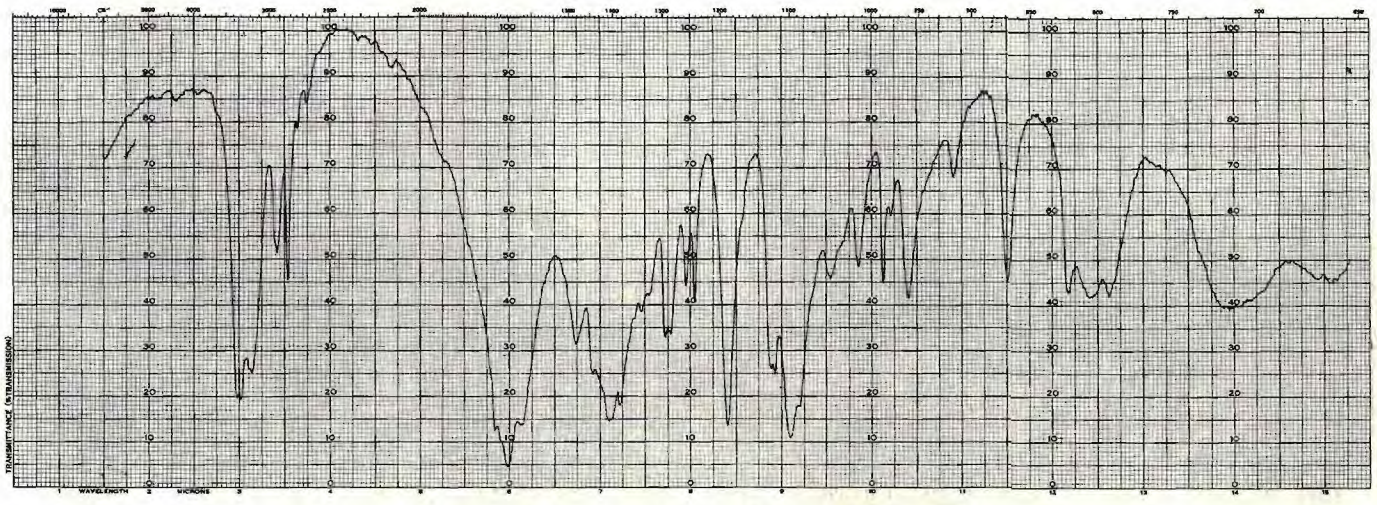

Figure 23. Tetrahydropyran-4-carbonylureide.

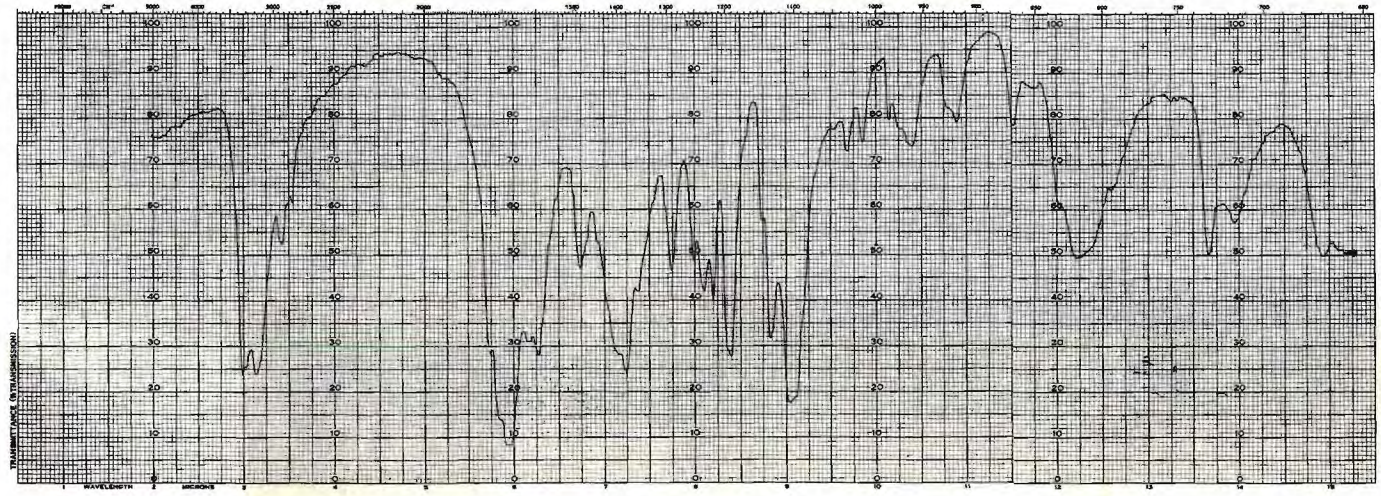

Figure 24. Tetrahydropyran-4-carbonylureide, Tetrahydropyran-4-carboxy-4-carbonylureide Mixture.

Figure 25. 5,5-Bis(2-iodoethyl)barbituric Acid.

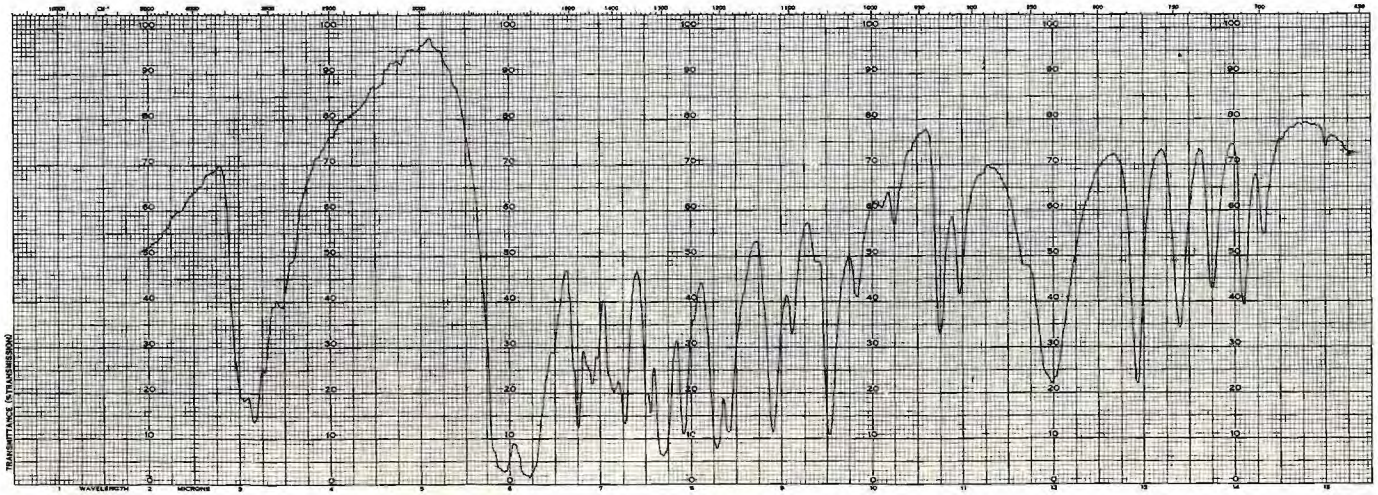

Figure 26. Spiro-1'-methylpiperidine-4',5-barbituric Acid.

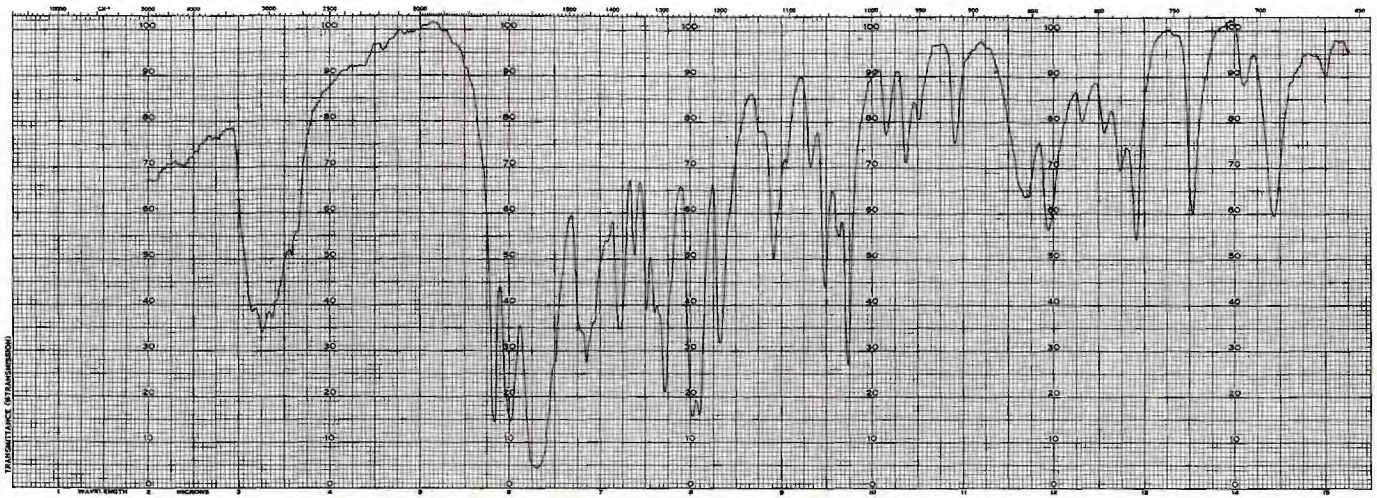

Figure 27. Spiro-1'-ethylpiperidine-4',5-barbituric Acid.

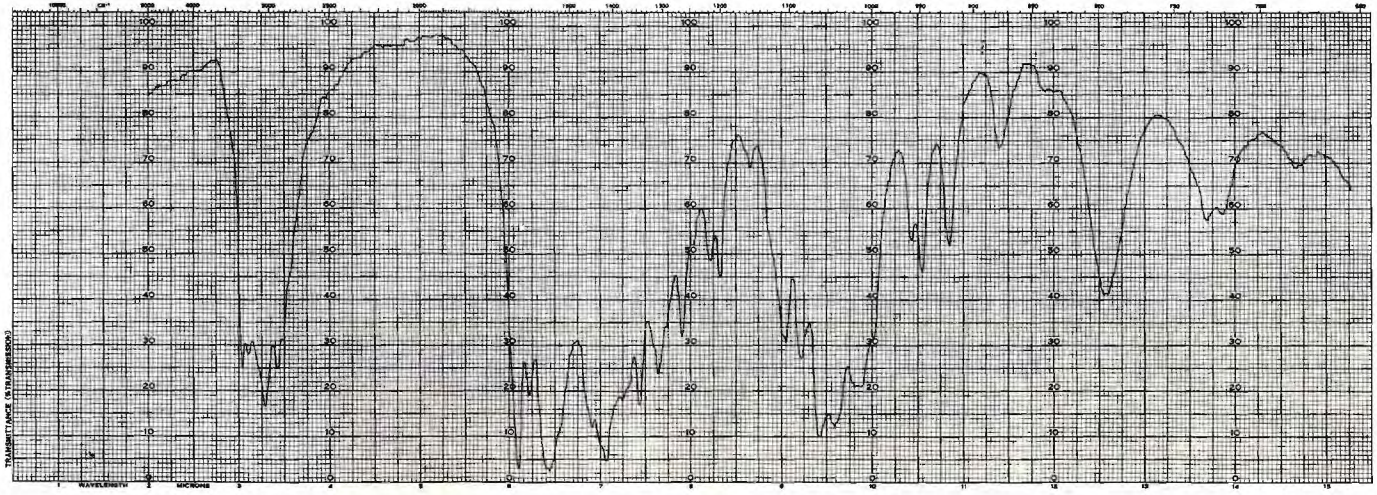

Figure 28. Spiro-1'-(2-hydroxyethyl)piperidine-4',5-barbituric Acid.

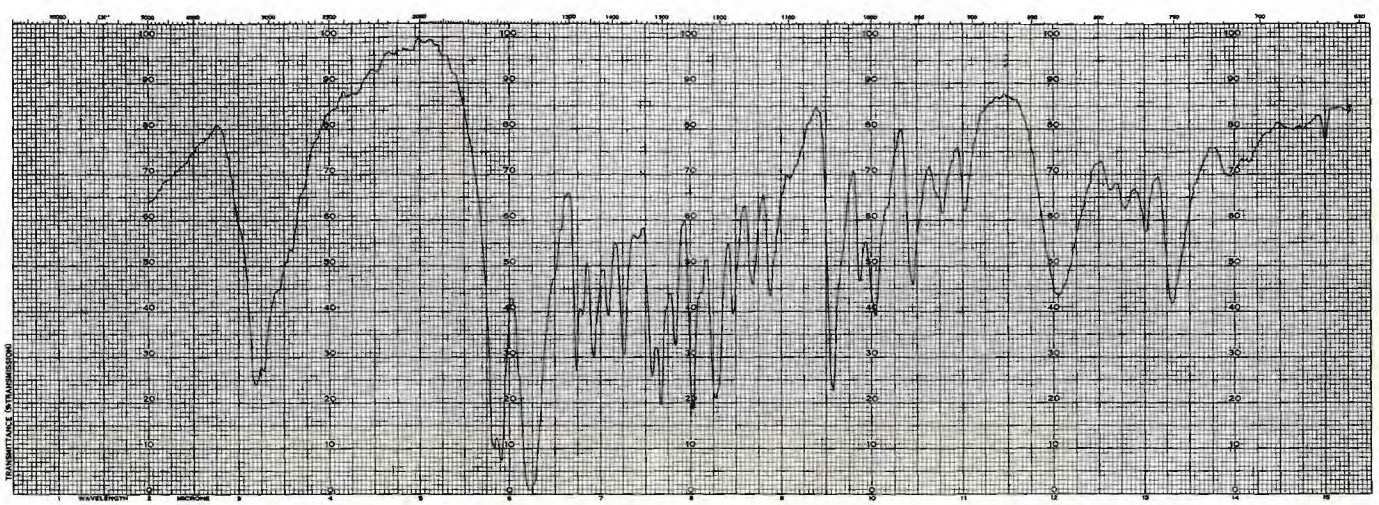

Figure 29. Spiro-1'-allylpiperidine-4',5-barbituric Acid.

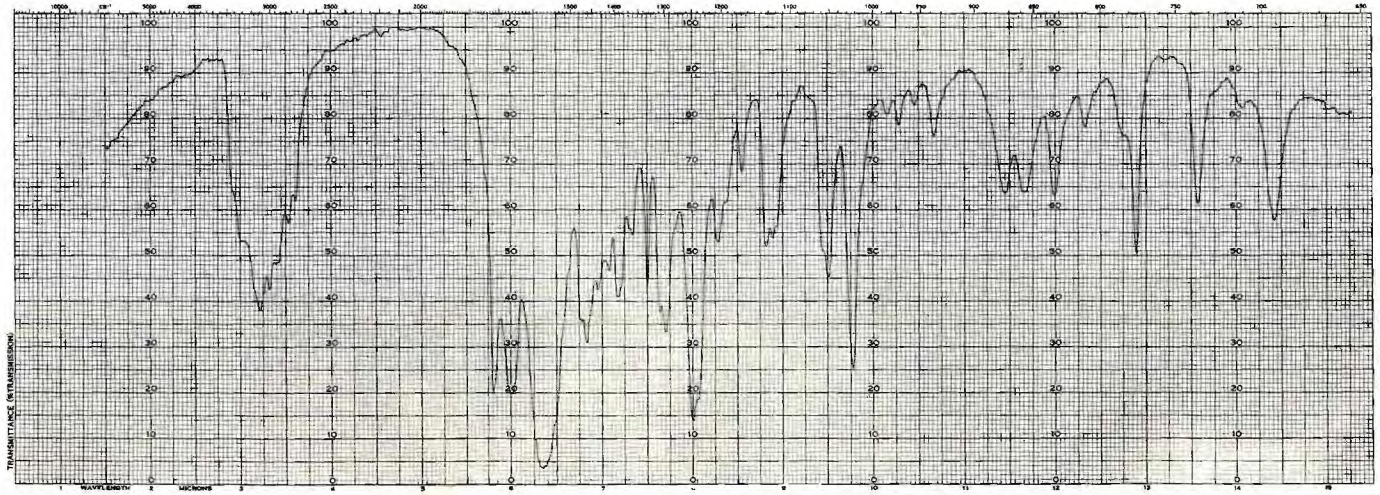

Figure 30. Spiro-1'-isopropylpiperidine-4',5-barbituric Acid.

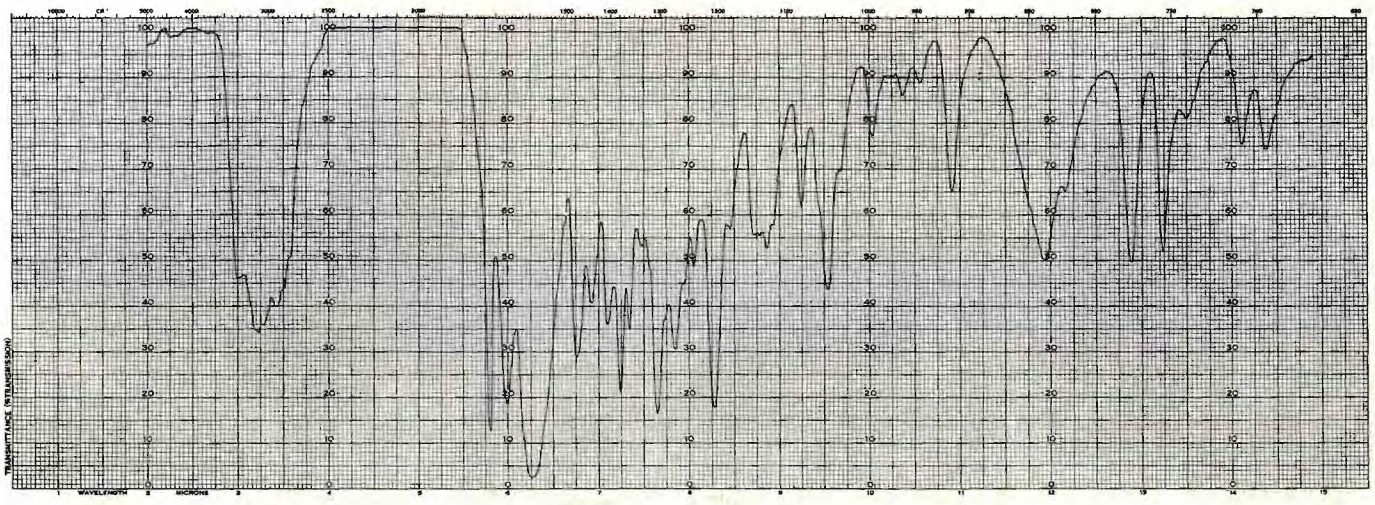

Figure 31. Spiro-1'-n-butylpiperidine-4',5-barbituric Acid.

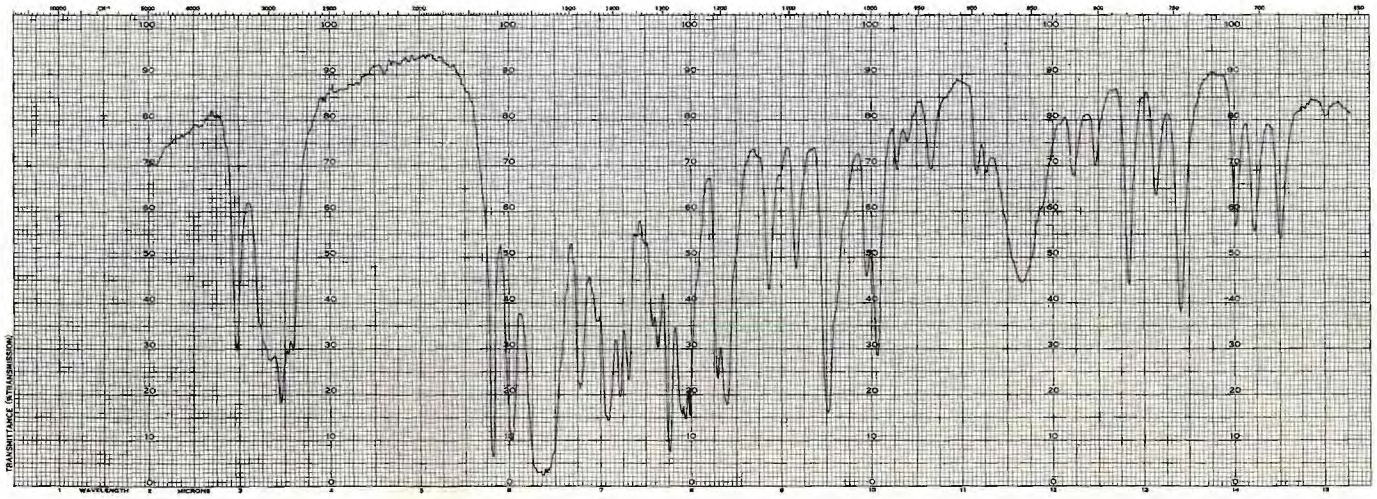

Figure 32. Spiro-1'-cyclohexylpiperidine-4',5-barbituric Acid.

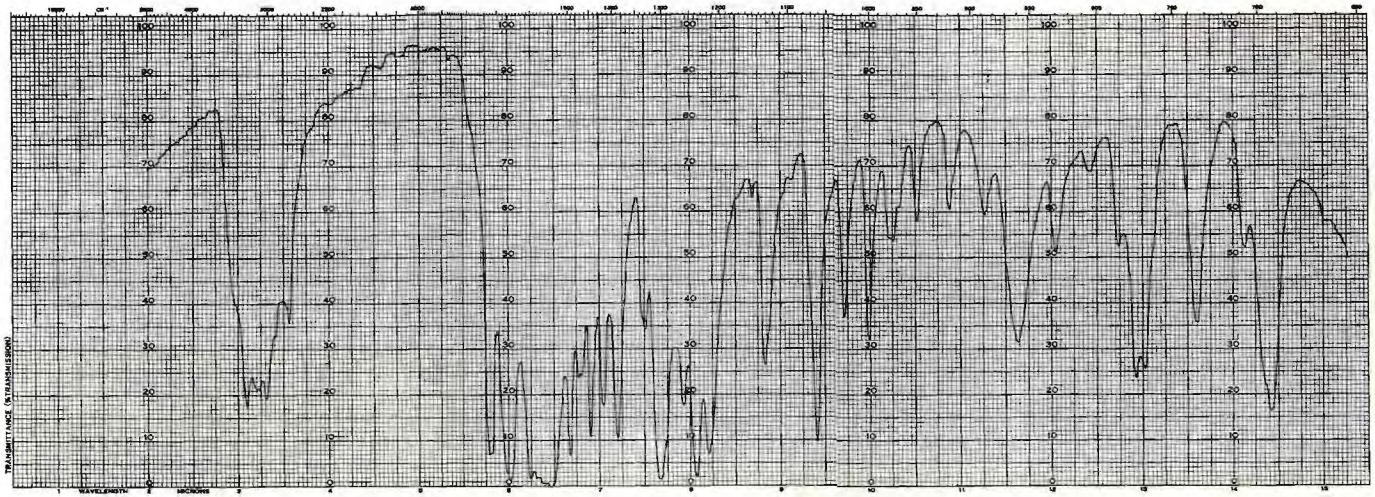

Figure 33. Spiro-1'-phenylpiperidine-4',5-barbituric Acid.

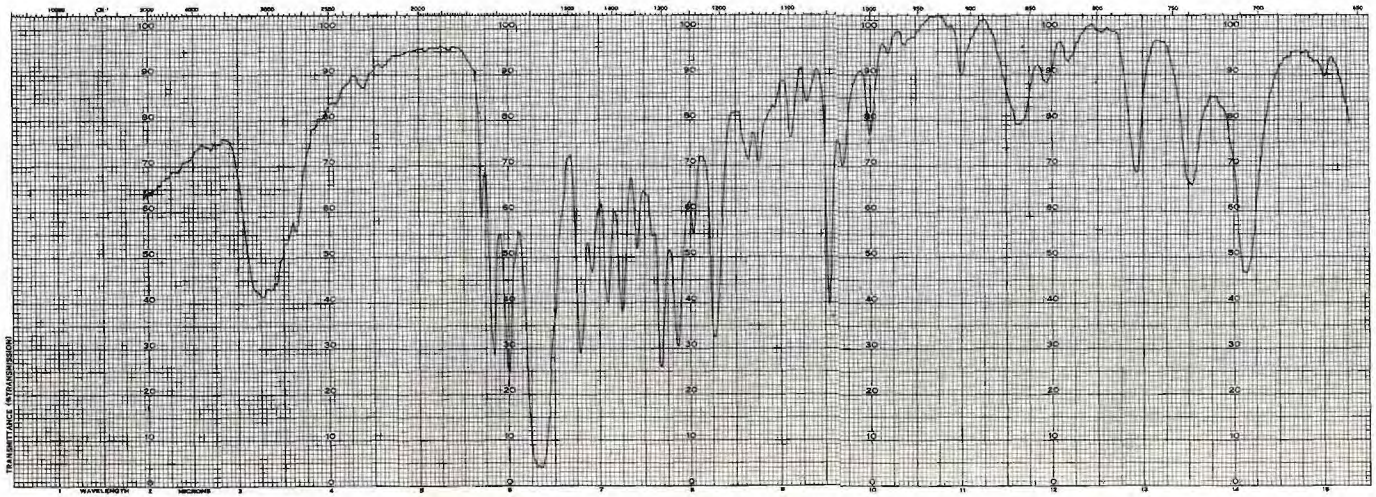

Figure 34. Spiro-1'-benzylpiperidine-4',5-barbituric Acid.

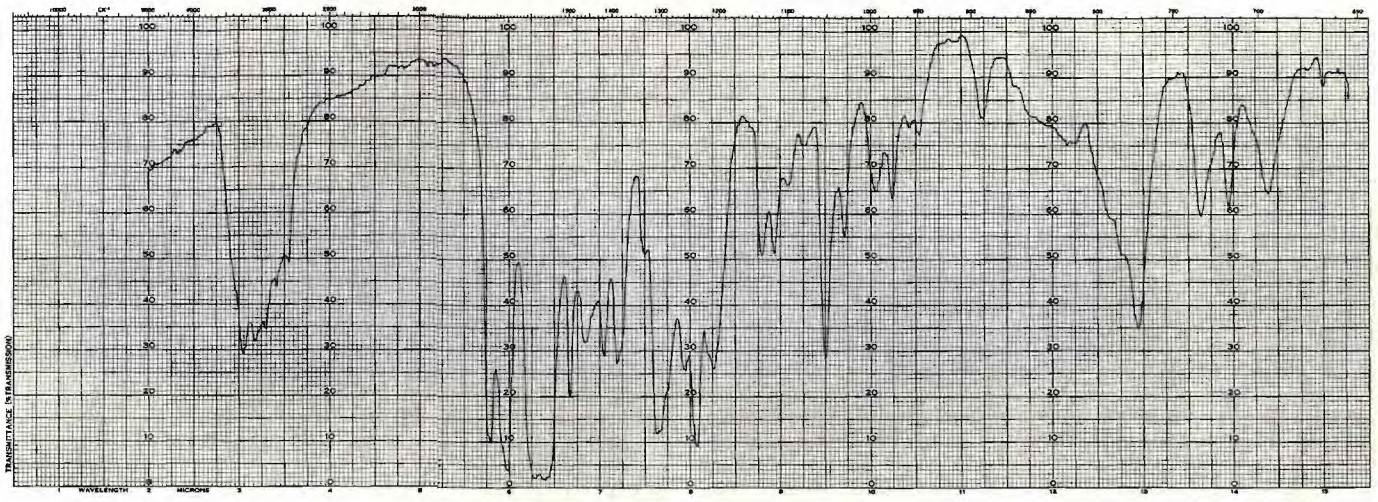

Figure 35. Spiro-1'-o-tolylpiperidine-4',5-barbituric Acid.

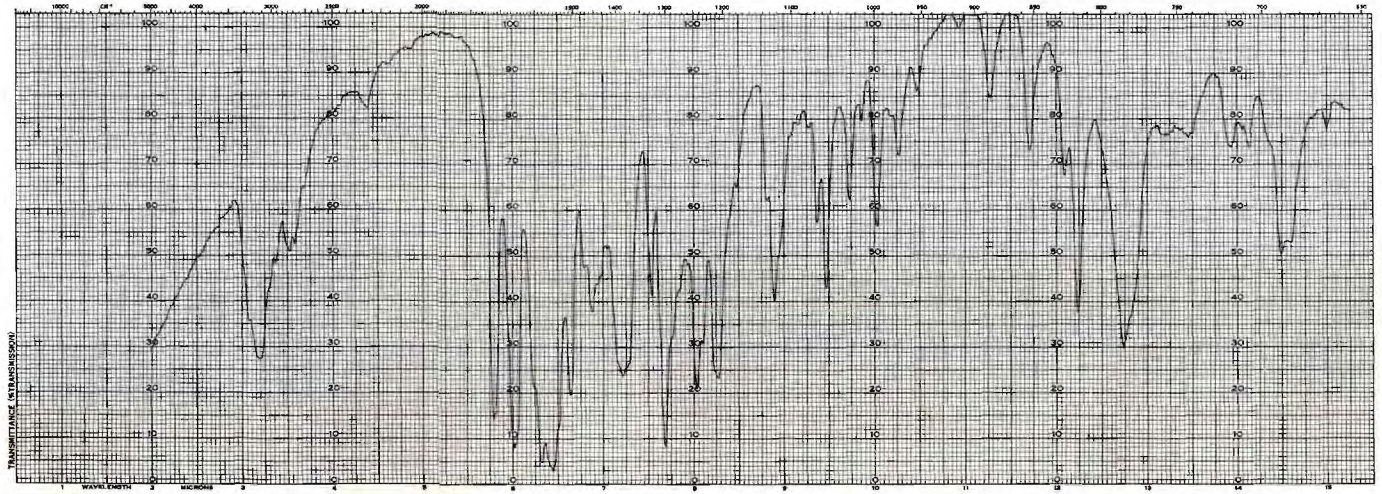

Figure 36. Spiro-1'-p-tolylpiperidine-4',5-barbituric Acid.

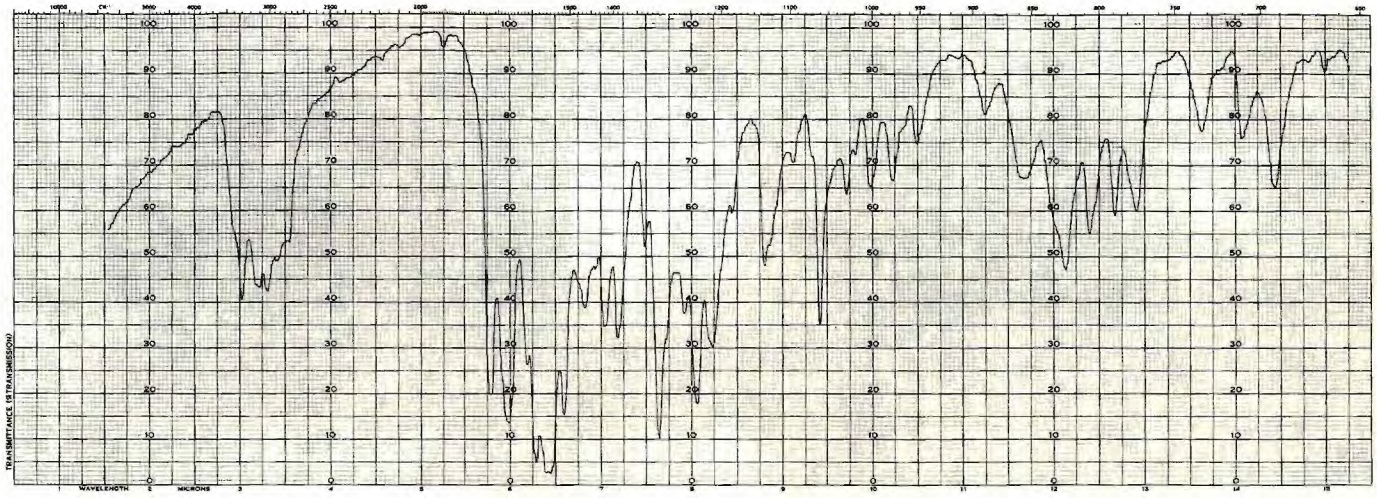

Figure 37. Spiro-1'-p-tolylpiperidine-4',5-barbituric Acid Hemixyleneate.

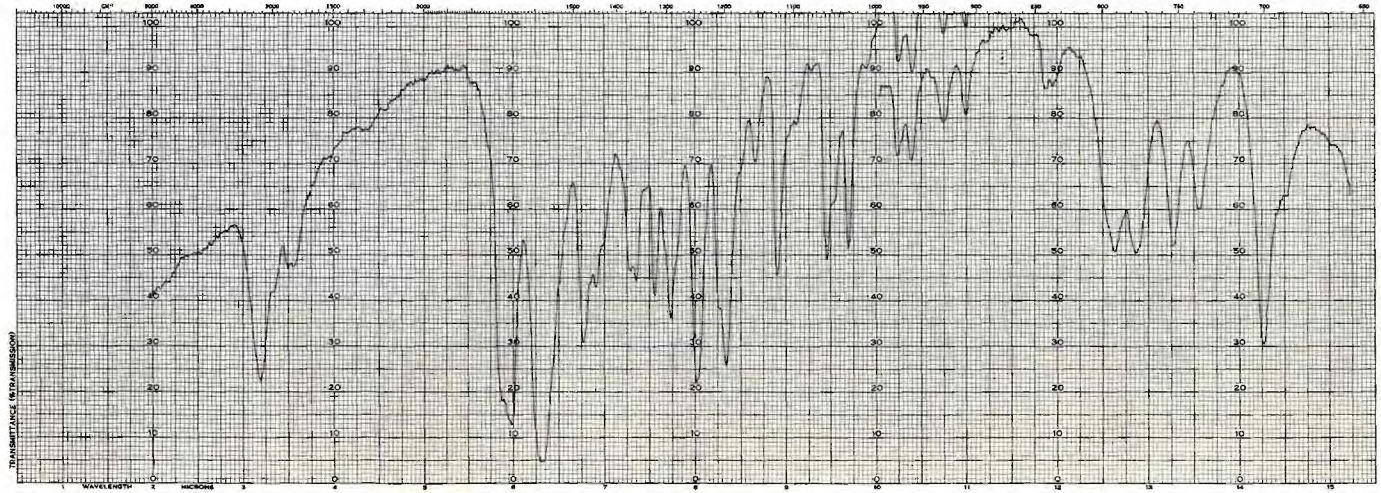

Figure 38. Spiro-1'-(2-phenylethyl)piperidine-4',5-barbituric Acid.

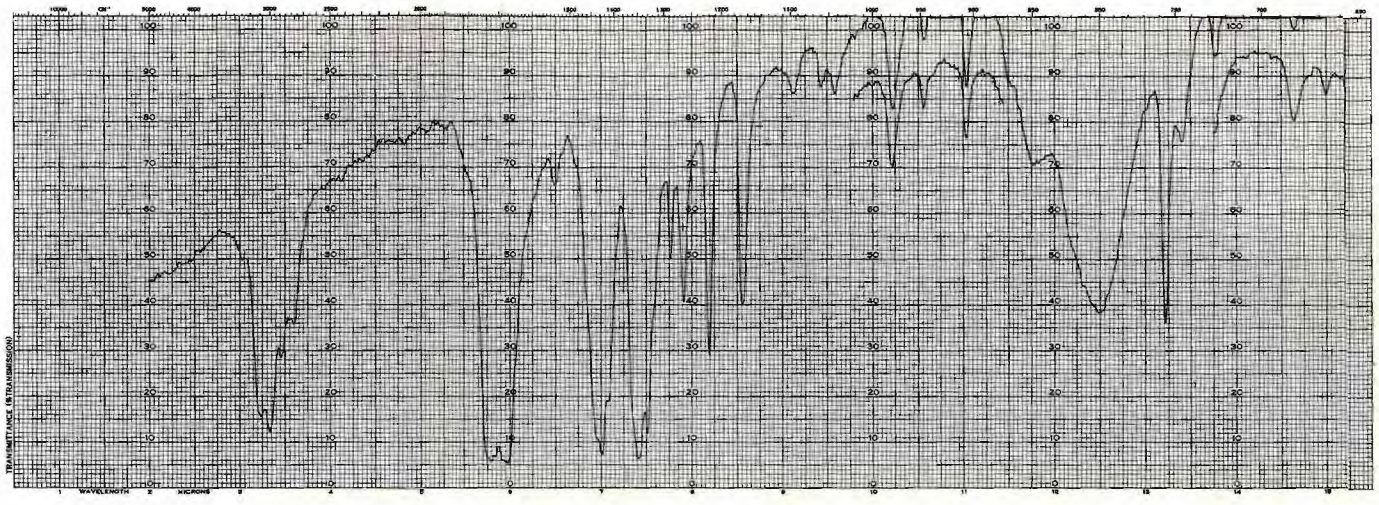

Figure 39. Spirocyclopentane-1',5-barbituric Acid.

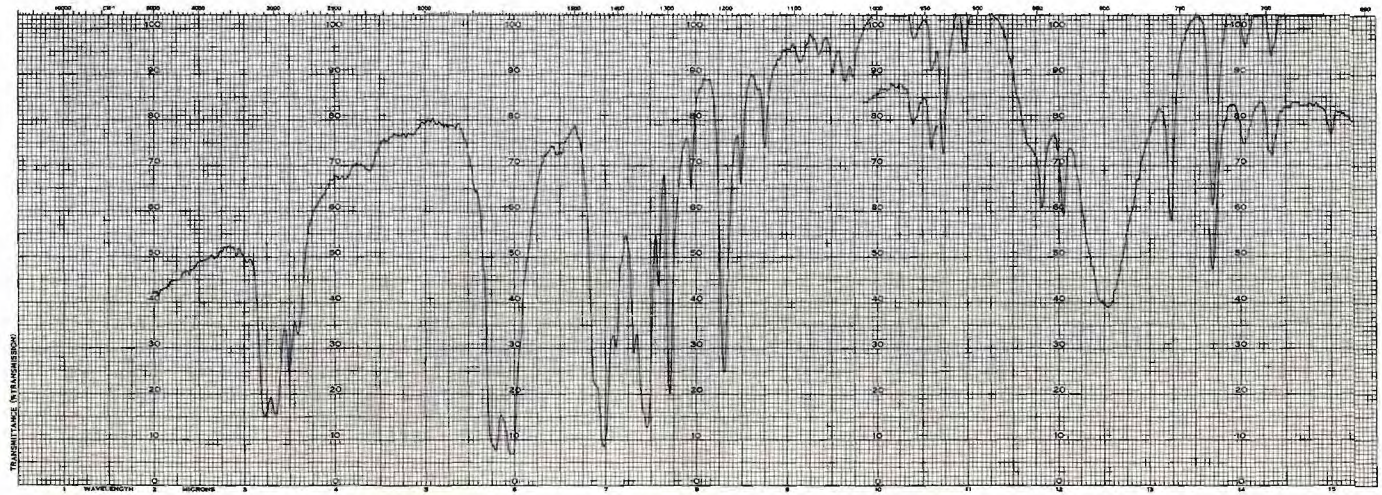

Figure 40. Spirocyclohexane-1',5-barbituric Acid.

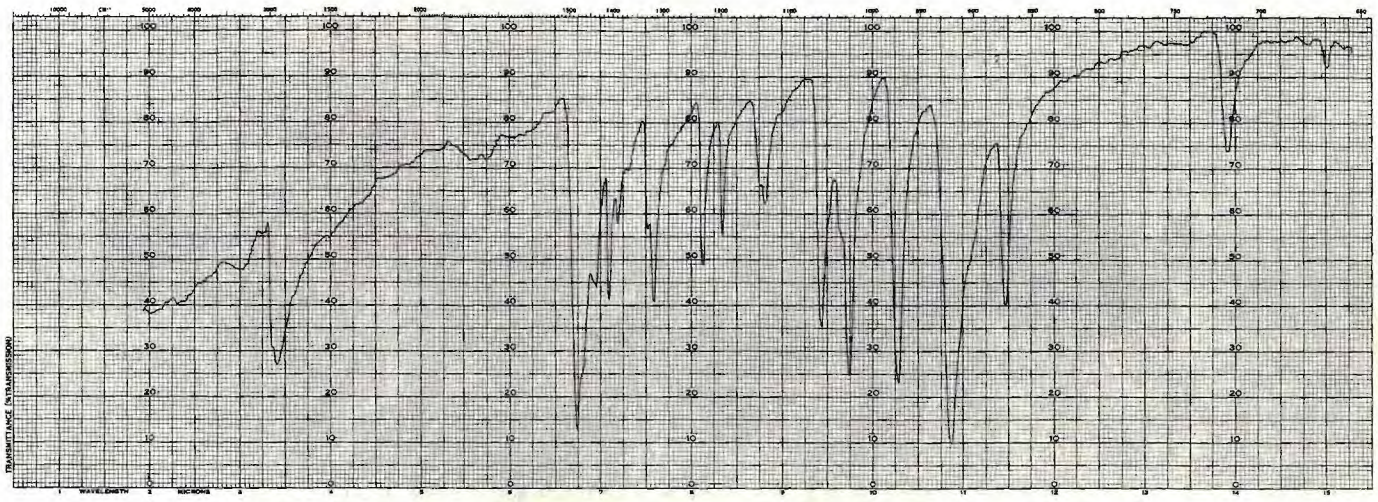

Figure 41. N,N,N',N'-tetramethylpiperizium Dichloride.

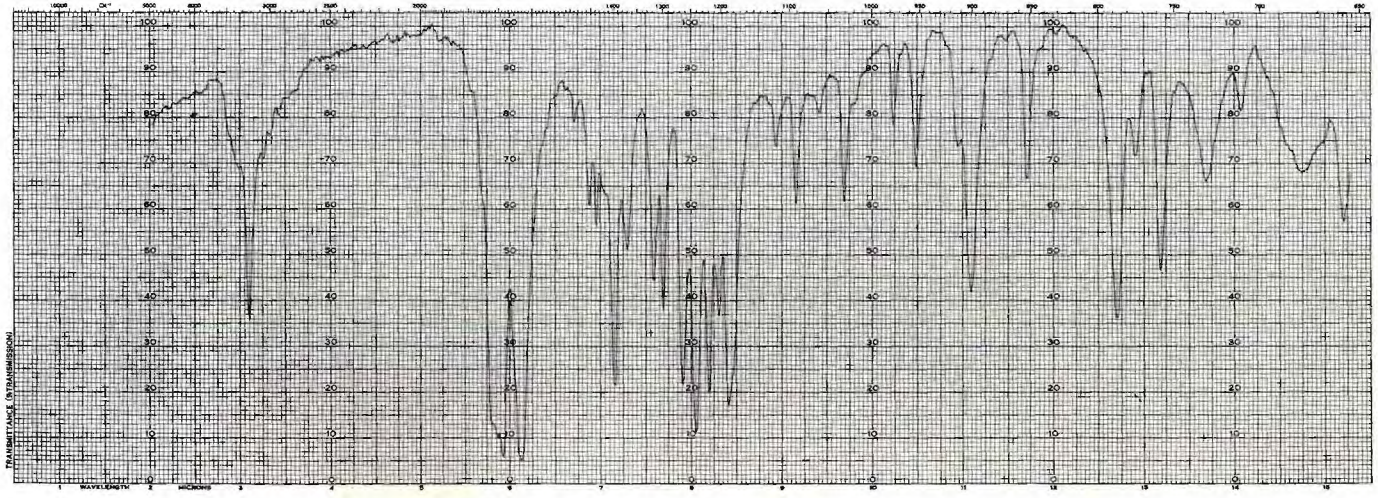

Figure 42. 5-(2-iodoethyl)-5-(2-carboxymethylaminoethyl)barbituric Acid.

Figure 43. Diethyl Tetrahydropyran-4,4-dicarboxylate.

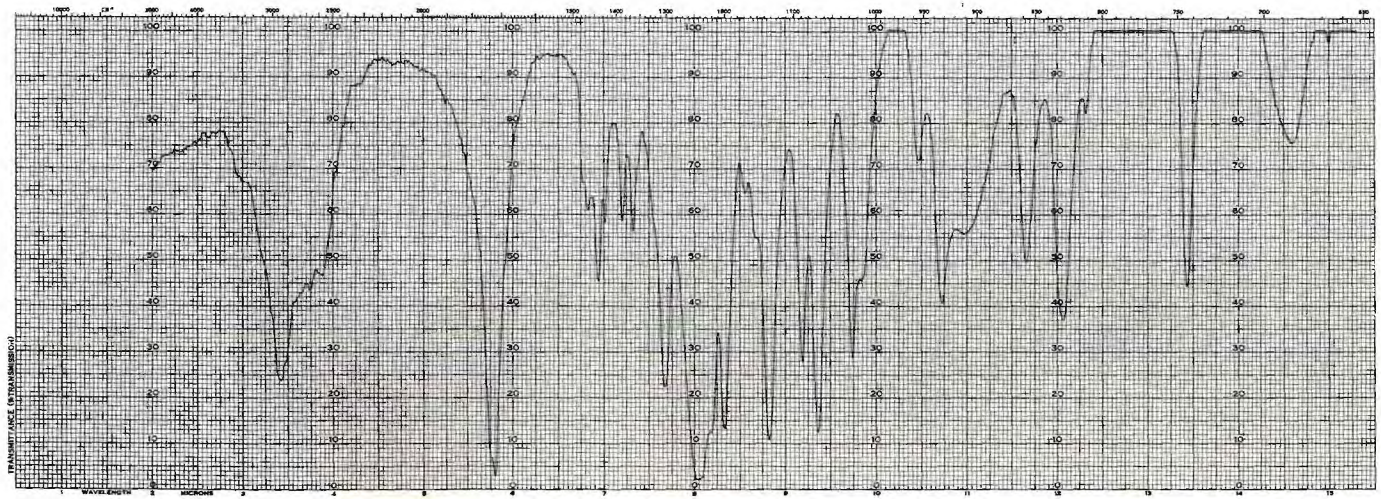

Figure 44. Ethyl Tetrahydropyran-4-carboxylic Acid-4-carbocylate.

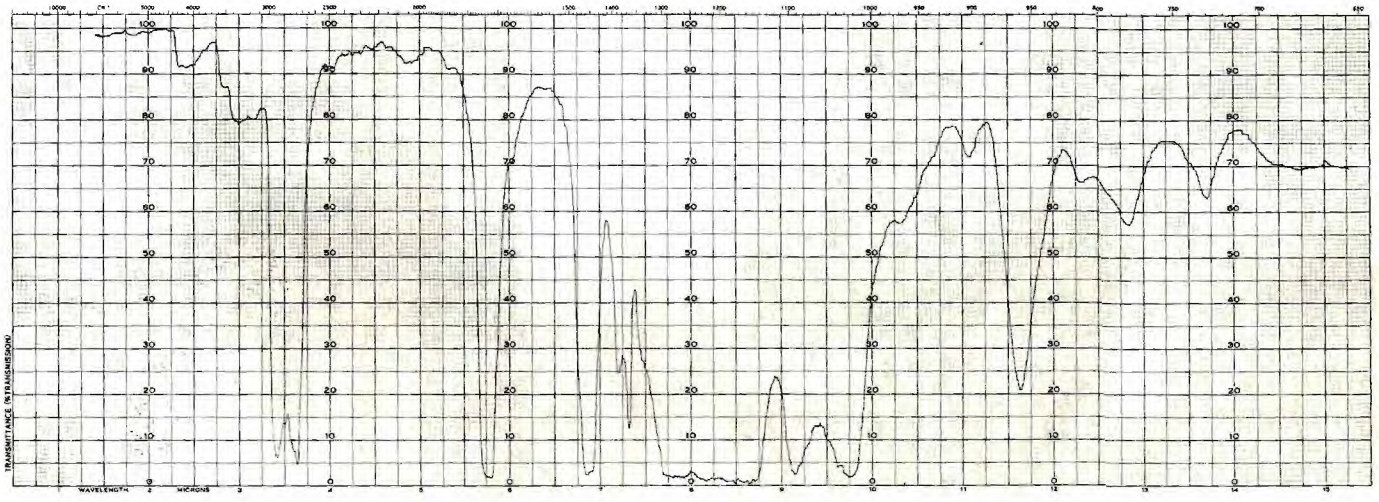

Figure 45. Diethyl Bis(2-dimethylaminoethyl)malonate.

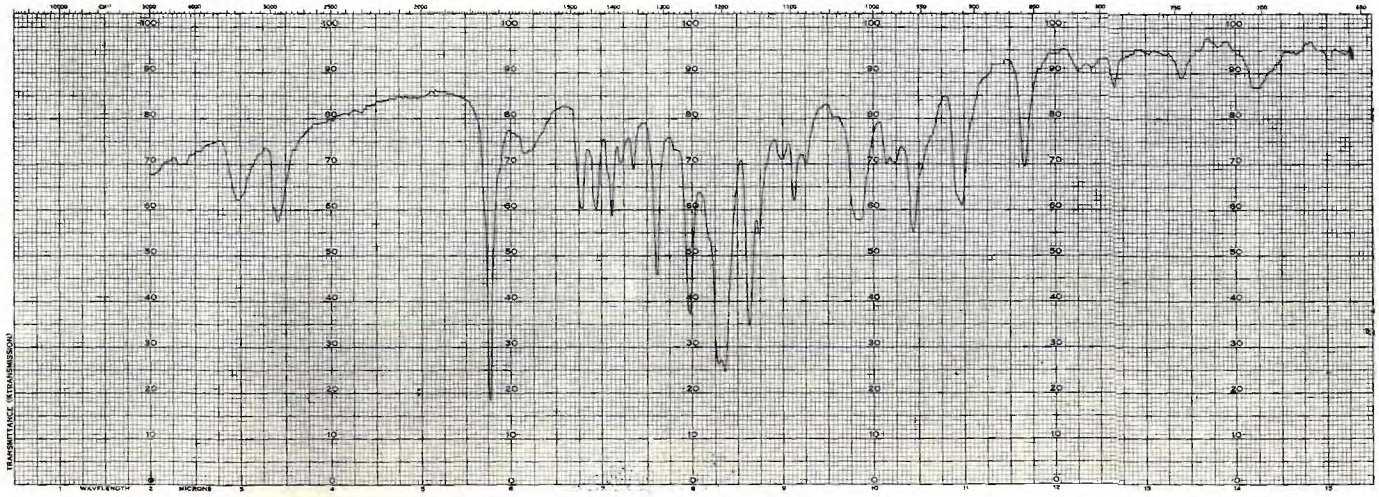

Figure 46. Diethyl Bis(trimethylethyleneammonium iodide)malonate.

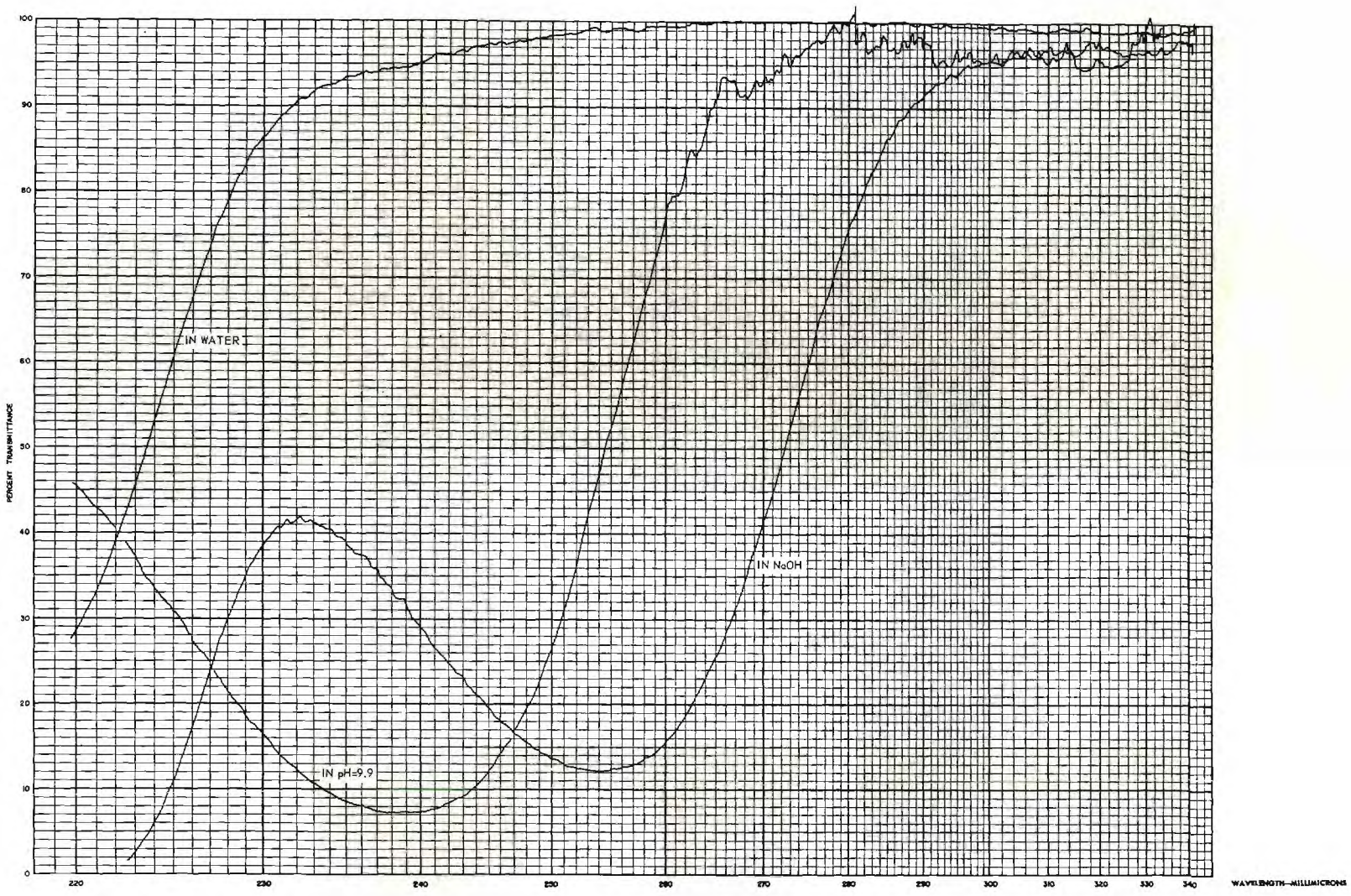

Figure 47. Ultraviolet absorption of 5,5-diethylbarbituric Acid.

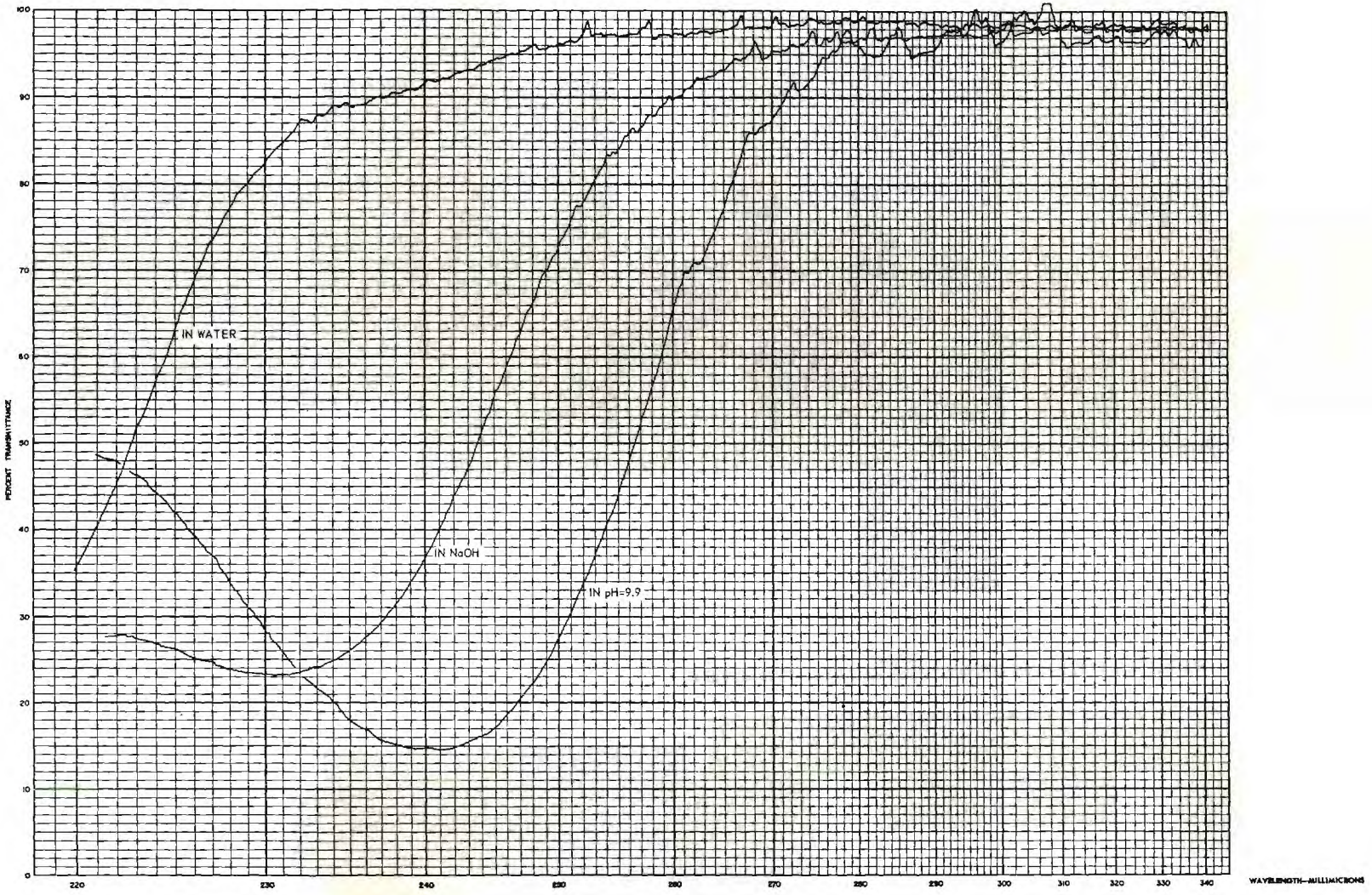

Figure 48. Ultraviolet absorption of Spirotetrahydropyran-4',5-barbituric Acid.

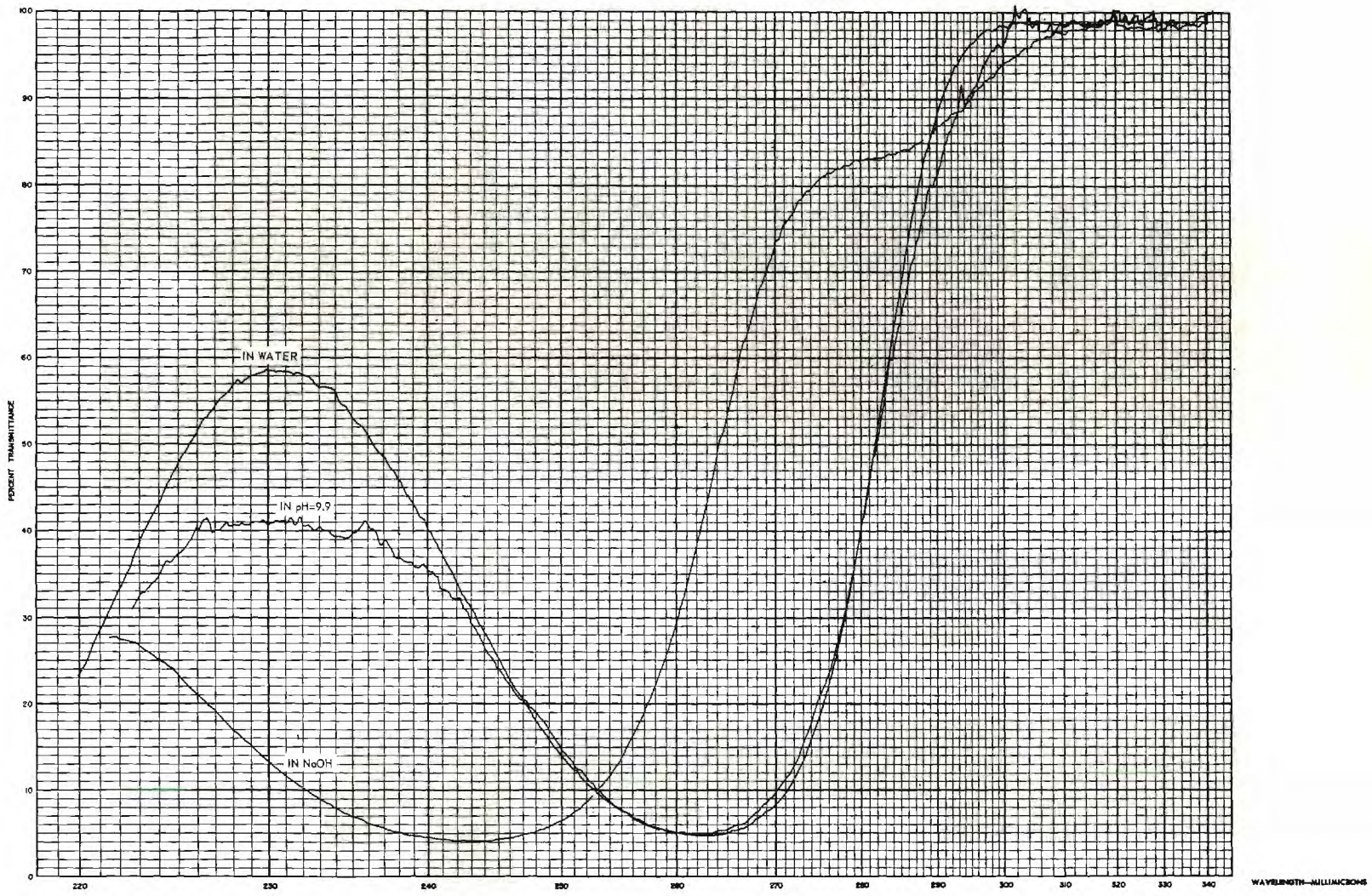

Figure 49. Ultraviolet absorption of Spiro-1'-methylpiperidine-4',5-barbituric Acid.

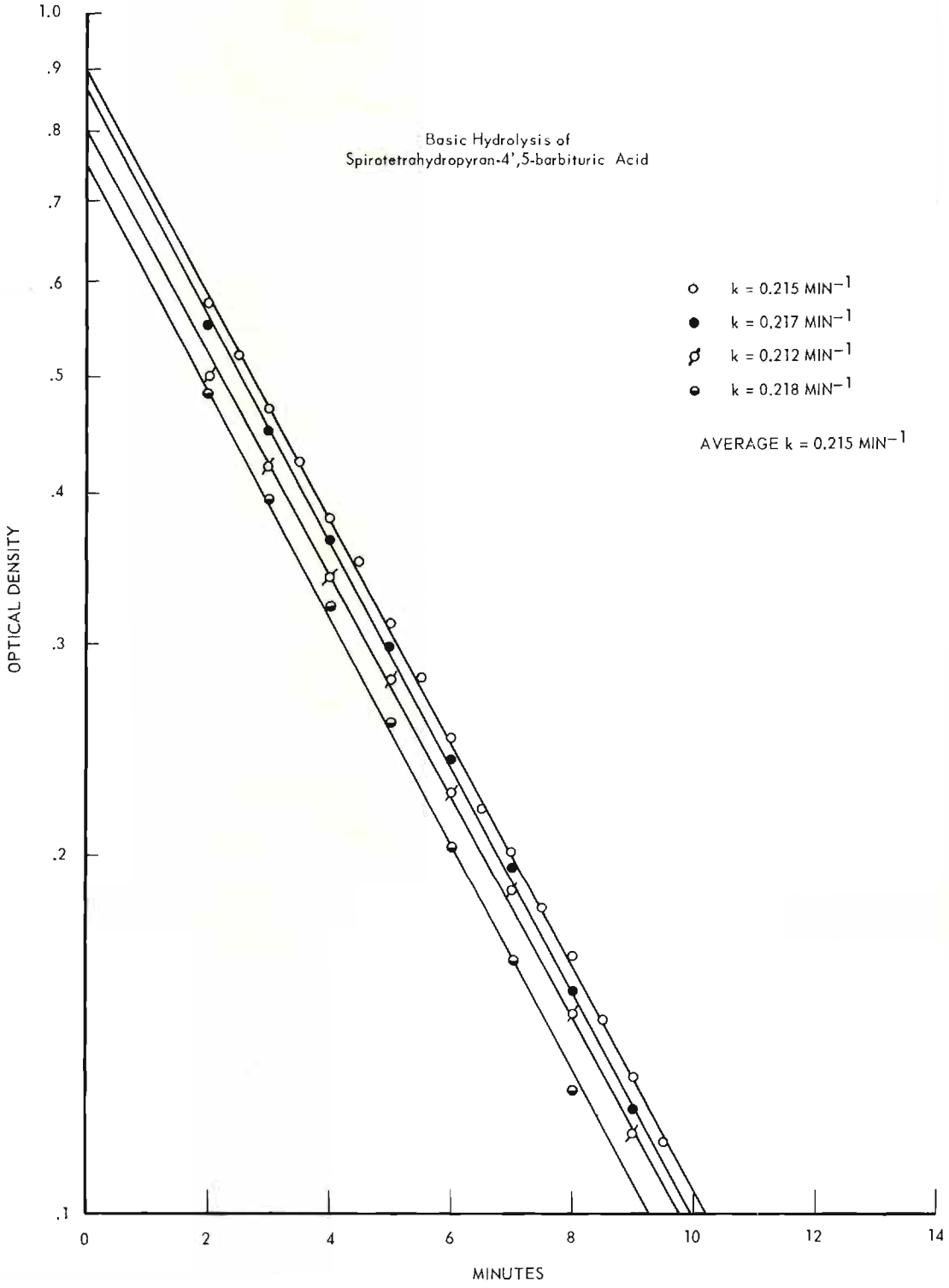

Figure 50. Sample Rate Curves.

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VITA

VITA

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He is a member of Sigma Xi, Phi Lambda Upsilon, the American Chemical Society, and the Georgia Academy of Science.

He is the father of four children who were born during the period of his study at Georgia Tech.